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Understanding the Neuroanatomical Basis of Executive Dysfunction in Medically Refractory Temporal Epilepsy

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UNDERSTANDING THE NEUROANATOMICAL BASIS OF EXECUTIVE DYSFUNCTION IN MEDICALLY REFRACTORY TEMPORAL LOBE EPILEPSY

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ABSTRACT

This study investigated the relationship between prefrontal cortex (PFC) volume and hippocampal sclerosis, and the extent to which each relates to executive functioning (EF) deficits in individuals with medically refractory temporal lobe epilepsy (TLE). Refractory TLE is one of the more common forms of epilepsy, and individuals with refractory TLE are at high risk for cognitive deficits. While memory impairments are common, individuals with refractory TLE often show deficits in a wide range of cognitive domains. The hippocampal and nociferous cortex hypotheses were tested to clarify the extent to which EF deficits are related to hippocampal sclerosis, reduced bilateral PFC volume, or some combination of the two. MRI and neuropsychological test data from 38 patients preparing for epilepsy surgery were analysed. Patients showed impairment on a composite measure of EF. There was no relationship between bilateral PFC volume, hippocampal volume ipsilateral to seizure onset, and any of the neurocognitive tests.

DEDICATION

First, to the Annes: Rebecca Anne, Dorothy Anne, and Ann Laurel;

Second, to my family;

Third, to the GLORY of GOD

Whose power, working in us, can do infinitely more than we can ask or imagine.

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LIST OF ABBREVIATIONS

ATLE	Anterior temporal lobectomy
BDI	Beck Depression Inventory
BOLD	Blood-oxygen-level dependence
EF	Executive functioning
CA1	Cornu Ammonis area 1
CD ROM	Compact disc read-only memory
CEO	Chief executive officer
CNS	Central nervous system
CT	Computerized tomography
CVLT	California Verbal Learning Test
DPFC	Dorsolateral prefrontal cortex
DTI	Diffusion tensor imaging
EEG	Electroencephalography
fMRI	Functional magnetic resonance imaging
IQ	Intelligence quotient
IRB	Institutional Review Board
JOLO	Judgment of Line Orientation Test
MMPI-2	Minnesota Multiphasic Personality Inventory-2
MRI	Magnetic resonance imaging
PCA	Principal Components Analysis
PE	Perseverative error
PFC	Prefrontal cortex
ROCF	Rey Osterreith Complex Figure test
ROI	Region of Interest
SPGR	Spoiled gradient echo sequences

T-2	Spin-spin relaxation time
TIV	Total intracranial volume
TLE	Temporal lobe epilepsy
TOMM	Test of Memory Malingering
VBM	Voxel based morphometry
WAIS-R	Wechsler Adult Intelligence Scale – Revised
WMS-R	Wechsler Memory Scale - Revised
WCST	Wisconsin Card Sorting Test
WSU	Wayne State University

CHAPTER 1

Introduction

The goal of this study was to investigate the possible association between prefrontal cortex (PFC) volume and medial temporal (hippocampal) sclerosis in individuals with medically refractory temporal lobe epilepsy (TLE). I sought to determine whether there is a relationship among prefrontal cortex (PFC) volume, medial temporal (hippocampal) sclerosis, and executive functioning (EF) deficits in these individuals. Performance on neuropsychological EF tests was considered in light of both hippocampal sclerosis and bilateral PFC volume. Results will help clinical neuropsychologists better understand the nature of EF deficits observed in individuals with medically refractory TLE, and will help inform and guide future treatment and rehabilitation for these individuals.

Defining Executive Functioning

The cognitive processes referred to as executive functioning are difficult to define. Burgess and Shallice (1997) write that EF is a cognitive *system* that acts in a supervisory capacity over other cognitive functions. Goldberg (2001) likens EF to a corporate CEO or the conductor of an orchestra. In Fuster's model, EF is defined as any action "in the time domain" which differs from an automatic routine or response (2008, p. 3). Baron (2004) uses a somewhat different approach, defining EF as

> The metacognitive capacities that allow an individual to perceive stimuli from his or her environment, respond adaptively, flexibly change direction, anticipate future goals, consider consequences, and respond in an integrated or common-sense way, utilizing all these capacities to serve a common purposive goal. Baron, 2004, p. 135

Lezak, Howieson, and Loring (2004) identify volition, planning, purposive action, and effective performance of necessary tasks as the four essential components of EF. Conversely, Anderson and her colleagues (2001) write that EF has three, rather than four, components: attentional control, cognitive flexibility, and goal setting. While we

may see some similarities among definitions of EF (e.g., goal-setting [Anderson et al.] and purposive action [Lezak et al.]) there remain important differences. For the purposes of this study, Baron's definition will be used. Cognitive shifting, updating, and inhibition (three components of EF examined by Miyake et al., 2000) will be the "metacognitive capacity[ies]" (Baron, 2004, p. 135) that will be examined in detail in this study.

Executive Functions Are Diverse

EF is not a unitary process. The tests that clinical neuropsychologists use to assess EF vary substantially (see Strauss, Sherman, & Spreen, 2006, for a discussion) reflecting the heterogeneity of executive functions. For example, the three most popular tests of EF used by clinical neuropsychologists are the Wisconsin Card Sort Test (WCST), the Rey Osterreith Complex Figure Test (ROCF), and the Halstead-Reitan Category Test (Rabin, Barr, & Burton, 2005). Given the different task demands of these three popular tests, it is no wonder that correlations among different tests of EF can be modest (e.g., $r \leq 0.40$; Collete, Hogge, Salmon, & Van Der Linden, 2006). Of further importance, the tests used to measure EF are not pure – that is, tests of EF necessarily assess other components of cognitive functioning as well (e.g., attention, language). For example, the ROCF requires an individual to attend to a complex figure for a certain period (attention), remember the figure (visuospatial memory), and then draw the figure from memory (motor skills). Thus, performance on EF tests is affected by other cognitive functions (Collete et al., 2006; Miyake et al., 2000).

Differentiating Executive Functions

The three-factor model. While the attempt has been made to differentiate components of EF, it is difficult to do so. In Miyake's three-factor model of EF, confirmatory factor analysis yielded three slightly correlated components (Miyake et al., 2000). The three factors that emerged were labeled shifting, updating, and inhibiting. Miyake and his colleagues (2000) defined shifting as the cognitive process of alternating

back and forth between mental sets or tasks; updating as the continual monitoring and revising of material in working memory; and inhibition as the ability to resist or suppress an automatic response (see Friedman & Miyake, 2004, for more discussion). Notably, all three components share core elements: for example, in order to shift successfully, an individual would also be required to update his or her mental set, and inhibit a pre-potent response.

Arguing against the theoretical separation of executive functions, Fuster (2003; 2008) decries the attempt to separate and discriminate between executive functions, and asserts instead that all executive functions are closely interrelated. He states that it is impossible to separate executive functions either on anatomical or functional grounds. For example, no single executive function has been successfully mapped to a single, specific area of cortex (Fuster, 2008). While some areas of the frontal cortex are more active than other frontal areas in tests of inhibition (e.g., the right inferior frontal gyrus; Aron, Robbins, & Poldrack, 2004) the parietal and temporal cortices are also active in these types of tests (Collete et al., 2006). Further, while some areas of frontal cortex are activated by tests of inhibition, these areas of cortex are also activated by other tests of EF (see Collete et al., 2006; discussion below). Fuster (2008) argues that no single subcomponent of EF is able to explain its general gestalt: for example, inhibition alone is unable to explain the monitoring and updating of material in working memory, nor does inhibition fully explain the ability to divide attention between one or more tasks.

Localizing Executive Functioning

Perhaps as controversial as the definition of EF is its localization. Neuropsychologists have long associated EF with the frontal lobes (see Andres, 2003; Fuster, 1993; Goldberg, 2001; Miller & Cohen, 2001; Strauss et al., 2006). In the 1960s, Luria (as cited by Andres, 2003) proposed a one-to-one relationship between EF and the frontal lobes, suggesting that the frontal lobes, and only the frontal lobes, were involved

in EF. While this perspective was at one time prevalent in the neuropsychological community (see Andres, 2003, for a discussion), the reciprocal connections between the frontal cortex and other areas of the brain are increasingly recognized and emphasized, both in research and clinical practice.

The prefrontal cortex. There are difficulties in localizing EF in specific regions of the frontal lobes, partially because the frontal cortex is the largest area of the brain, containing over one third of total neocortex (Fuster, 1993; Toone, 1998). The frontal lobes are made up of numerous sub-regions (McPherson & Cummings; 1998; Middleton & Strick, 2001). The largest area of the frontal lobe is the prefrontal cortex (PFC), which lies anterior to the motor, premotor, and limbic areas (Blumenfeld, 2002). The PFC has connections with other areas of the cortex and subcortex. The PFC also plays an important role in integration of information from the limbic system: it has multiple bidirectional connections with the limbic system and the hippocampus in particular (Blumenfeld, 2002; Fuster, 2008; Middleton & Strick, 2001).

PFC and EF. Both neuroimaging and neurophysiological data have lent support to the view that EF can be localized (at least in part) in the PFC (see Fuster, 2008, for an extensive review of data from humans and other primates). Studies of cognitive control have suggested that this executive function requires activation of PFC networks. Based on both neuroimaging and electroencephalography (EEG) data, Miller and Cohen (2001) assert that cognitive control takes place in the PFC and that it is the primary role of that cortical area. For example, when a participant is planning and programming a future action (but, notably, not yet performing it), both fMRI and other neuroimaging (e.g., CT with carotid angiography) data show activation in the human PFC (e.g., Danker & Anderson, 2007; Roland & Friberg, 1985). Fuster (2008) writes that this is evidence for PFC involvement in the tracking and integration of temporally distinct objects or actions. Functional imaging studies in both humans and animals have also shown PFC activation

in working memory tasks, in the encoding of new information in relation to previously existing cognitive schemas, and in cognitive shifting. The PFC is active in EF tasks.

Evidence for PFC involvement in EF tasks is also seen in data from patients with other types of pathology (Mendez & Cummings, 2003; West & Grace, 2001). For example, structural neuroimaging studies involving individuals with schizophrenia have shown significant PFC volume reduction (atrophy) in both grey and white matter (Bonilha et al., 2008; Harvey et al., 1993; Schlaepfer et al., 1994; Weinberger & Berman, 1998). EF deficits in schizophrenia are associated with low counts of pyramidal cells and fewer interneurons in the PFC (Benes, as cited by Fuster, 1993; Fuster, 2008). Taken altogether, this evidence has led some to suggest that EF deficits in schizophrenia and other disorders are due to structural abnormalities (specifically, reduced PFC volume) and a resulting disturbance in the dorsolateral prefrontal-medial temporal limbic circuit (Lichter & Cummings, 2001; Weinberger, Berman, Suddath, & Torrey, 1992).

EF and extrafrontal regions. Although EF may have been partially localized to the PFC, other data suggest this is not the whole story. While EF deficits may be seen after lesions in the PFC, deficits in EF may also result from lesions in other areas, including other regions outside the frontal lobes (Andres, 2003; Treitz, Daum, Faustmann, & Hasse, 2009). Individuals with frontal lobe lesions may *not* show executive functioning deficits, and vice versa (Schneider & Gutbrod, 1999), and some have even reported that EF deficits are more common after diffuse brain damage rather than damage limited to the PFC (Andres, 2003; Andres & Van der Linden, 2000; Collete et al., 2006; Cowey, & Green, 1996).

To further investigate the areas of the brain associated with EF, Bockova, Chladek, Jurak, Halamek, and Rektor (2007) used intracerebral depth electrode recordings to examine brain activation in neurosurgical candidates during an EF task (random letter generation). Data showed neural activation in areas of the frontal cortex

(including the PFC), as well as in the superior and medial *temporal* cortex during this task (Bockova et al., 2007). Specifically, the temporal cortex was especially active over the central and anterior middle temporal gyrus, as well as the central superior temporal gyrus. Thus, in more verbally mediated EF tests, not only the frontal lobes but also regions of the temporal lobes were activated.

Andres (2003) reviewed both neuroimaging and lesion studies and found that many common tests of EF (e.g., the WCST and the Stroop test) are not specifically sensitive to the PFC: rather, individuals with injuries in posterior and temporal regions can also do poorly on these tests. Recall that tests of EF necessarily require other components of cognitive functioning. Andres concluded that in addition to the frontal cortex (and specifically the PFC), the parietal cortex, basal ganglia, and medial and lateral temporal lobe, are involved in EF (Andres, 2003), at least partially because EF incorporates other cognitive functions.

In a comprehensive review of the literature, Collette et al. (2006) examined functional neuroimaging studies that have investigated the localization of EF in the brain, examining the EF factors outlined by Miyake et al., (2000). Results suggest that different but overlapping areas of the brain are involved in updating, shifting, and inhibiting (Collette et al., 2006). Shifting is associated with increased activation in both the posterior (e.g., parietal lobe) and anterior (i.e., bilateral dorsolateral PFC) regions of the brain (Loose, Kaufmann, Tucha, Auerb, & Lange, 2006). Updating is associated with increased activation in the dorsolateral PFC, inferior frontal and cingulate frontal cortex, as well as superior and posterior parietal areas. Finally, tasks requiring cognitive inhibition have been found to activate numerous regions of cortex including the cingulate cortex, PFC, and parietal and temporal cortices. As such, imaging data suggests that the frontal, parietal and temporal lobes are all involved in EF.

EF and distributed neural networks. The heterogeneity of executive functions is reflected in the heterogeneity of neural activation during EF tasks. It may be most accurate to say that EF is the product of distributed neural networks, or groups of neurons spread throughout the brain that work together to perform these functions. For example, Fuster has postulated that bidirectional connections between prefrontal and parietal cortices are involved in complex cognitive tasks (Quintana & Fuster, 1993):

> The parietal cortex, in addition to the prefrontal cortex, can be assigned a role in certain visuospatial aspects of cross-temporal integration. This integration is presumably mediated through bidirectional pathways connecting the two cortices … apparently certain sub-areas of the prefrontal cortex receive parietal afferents of functional importance for cross-temporal visuomotor behaviours. (Quintana & Fuster, 1993, p. 130)

Fuster's work with rhesus monkeys led him to suggest that a distributed neural network may best explain EF in humans. His model of EF (1993; 2008) posits a cyclical, ongoing interaction between different cortical areas (prefrontal, parietal, and temporal), in response to internal and environmental demands. Fuster sees the role of the PFC to be the organization of goal-directed, temporally oriented action (Fuster, 2008). Importantly, his very definition of the PFC as the "part of the [frontal] cortex that receives projections from… the thalamus" (2008; p. 2) necessarily emphasizes the role of neural networks. Impaired EF may thus result from synchronization among distal neural structures. So, although research suggests that EF may be primarily localized to the frontal lobes, the data also show that other areas of the brain are involved in EF.

Executive Functioning and Everyday Life

While we may wonder why such effort has been given to the research of a concept that lacks even a consensual definition, the importance of executive functions in daily life is widely recognized. Problems with EF may include difficulty planning in advance, selecting an appropriate course of action among diverse possibilities, ignoring extraneous stimuli, or solving problems: an individual may have difficulty living

independently, making sound decisions about personal and financial affairs, and maintaining meaningful relationships. These difficulties exemplify executive *dys*function, which is defined as generalized deficits in cognitive flexibility, organization, and self-monitoring (Ozonoff, 1998). Importantly, intact EF and executive dysfunction are not two sides of the same coin. Deficits in EF manifest with both negative and positive symptoms: that is, these individuals both *lack* certain cognitive abilities (e.g., self-monitoring) and *possess* unusual cognitive symptoms (e.g., confabulation). For example, in addition to deficits in verbal fluency, and poor performance on inhibition tasks, individuals with executive dysfunction may exhibit *witzelsucht*, or inappropriate humour, confabulation, or utilization behaviours (Blumenfeld, 2002).

The neuropsychological literature is rife with examples of individuals with executive dysfunction who are unable to live outside of a hospital, sustain gainful employment, or whose relationships disintegrate (see Kolb & Whishaw, 2009). Given the importance of executive functions in daily life, it is imperative for neuropsychologists to assess executive functioning in all clients, not just clients with frontal lobe lesions. For example, it is vital that executive functions be assessed in individuals who have seizures (Trimble, 1998).

Epilepsy and Seizure Disorders

The psychological and behavioural consequences of epilepsy have been the focus of study since the mid 19th century, when European psychiatrists began publishing about the psychopathology of their epileptic patients (Trimble, 1998). Falret (1859) and Griesinger (1868) both wrote about cases of inter-ictal psychosis in their patients. Later psychiatrists made comparisons between the inter-ictal psychosis of their patients with seizures and patients with schizophrenia (Trimble, 1998). Certainly, behavioural changes are common in individuals with epilepsy, especially temporal lobe epilepsy (see below; also Jeffreys & Mellanby, 1998; Shulman, 2000). These behavioural changes

include personality changes, changes in sexuality and sexual functioning, hyper-religiosity, and hypergraphia (Blumer, 1999; Trimble, 1998). It may be that these behavioural changes are linked to dysfunction in the limbic system, which includes diverse cortical structures from both the medial and ventral regions of the cerebral hemispheres, and is associated with emotion, sexual and basic survival behavioural patterns, motivation, and learning (Sherwood, 2003). The limbic system has, not surprisingly, extensive connections to other areas of subcortex (e.g., brain stem, diencephalon), as well as to the PFC.

Epilepsy is a condition characterized by recurrent, unprovoked seizures (Anderson et al., 2001; Teeter-Ellison & Semrud-Clikeman, 2007), which are periods of abnormal, excessive, or hyper-synchronous discharges of cortical neurons (Fisher et al., 2005). This abnormal and excessive cortical activation often results in distorted perception, movement, cognition, and loss of consciousness (Thompson & Trimble, 1996). The mechanism by which seizures are generated varies based on the underlying etiology of the seizure disorder. As Davis and his colleagues (2005) write, "it is important to remember that seizures [are] a symptom and not a disease" (p. 155). While epilepsy is associated with varied neuropathology, all etiologies share a common pathway of increased neural excitability and decreased neural inhibition in the area of epileptogenesis, or the area of epileptic focus (Davis, King, & Schultz, 2005). Several comprehensive surveys of epilepsy and seizure disorders are available (e.g., Trimble & Schmitz, 2002), and various classifications of types of epilepsy exist, based on location of epileptogenesis, seizure type, and/or laboratory (e.g., EEG) findings (Fisher et al., 2005). Some seizures are isolated to a particular area of the cortex (partial seizures) while other seizures begin in a specific cortical area and then spread outwards (generalized seizures; Fisher et al., 2005).

Medically Refractory Temporal Lobe Epilepsy

EF in medically refractory TLE is the focus of the current study. Medically refractory epilepsy is defined as epilepsy that does not respond to medication or other types of palliative treatment. These individuals often fare worse than their peers who experience seizure remission (Teeter-Ellison & Semrud-Clikeman, 2007) as they commonly experience generalized cognitive decline, regardless of epileptic focus (Chapman Black et al., 2010; Hermann, Seidenberg, Lee, Chan, & Rutecki, 2007; Lee & Clason, 2008; Strauss et al., 2006; Teeter-Ellison & Semrud Clikeman, 2007). TLE is the most common form of medically refractory epilepsy (Engel, Wilson, & Lopez-Rodriguez, 2002; Lee & Clason, 2008; Trimble, 1998). In an early meta-analysis, Trimble found that over three-quarters of all epilepsies were medically refractory TLE (Trimble as cited by Trimble, 1998).

Any diagnosis of epilepsy is associated with a 2- to 3- fold increase in mortality (Chadwick, 1994). Psychiatric sequelae and cognitive impairments are also fairly common in these individuals (Dodrill, 2008). The exact nature of the cognitive impairments seen in individuals with epilepsy is linked to the area of the epileptic focus (Lee & Clason, 2008). For example, deficits in memory are often found in individuals with temporal lobe epilepsy.

TLE is a form of focal epilepsy, that is, a type of epilepsy characterized by partial seizures. For the purposes of this study, TLE was defined as a medical disorder characterized by recurrent epileptic seizures, generated in one or both medial temporal lobes of the brain. TLE seizures that begin in the medial temporal lobe are characterized by loss of consciousness, unresponsiveness, and automatisms (Blumenfeld, 2002), of which lip smacking and hand and leg gestures are the most common. Because the temporal lobe shares multiple connections with other areas of the brain, partial seizures in this area of cortex often become generalized. Various subtypes of TLE have been studied, including medial and neocortical (lateral) TLE (Lee & Clason, 2008). Neocortical

TLE is characterized by seizures generated (or which have their focus) in lateral temporal structures (e.g., in the superior temporal sulcus and other neocortical areas). Medial TLE refers to epilepsy with epileptic focus in the temporal *sub*cortex: that is, the hippocampus, amygdala, and entorhinal cortex. Subcortical temporal regions are very susceptible to insult and injury (e.g., hypoxia), and, as a result, medial TLE is much more common than lateral TLE (Lee & Clason, 2008).

Hippocampal sclerosis. The most common etiology of medically refractory TLE is medial temporal sclerosis (Davis et al., 2005; Lee & Clason, 2008; Trimble, 1998). Medial temporal sclerosis is a common result of early insults to the CNS, such as hypoxia or febrile seizures (Davis et al., 2005), and occurs when there is a loss of neurons (and subsequent gliosis) in and around the hippocampus, amygdala, and entorhinal cortex (Davis et al., 2005). Trimble (1998) notes that medial temporal sclerosis affects primarily the "sub-fields of the hippocampus" (p. 238), and thus the term is often used interchangeably with *hippocampal* sclerosis. Hippocampal sclerosis can be identified using structural neuroimaging techniques: it can be seen as a hyper-intensity of the hippocampus on T-2 weighted magnetic resonance imaging (MRI) scans (Davis et al., 2005). Diagnostic work-ups for individuals with complex partial seizures often include MRI scans with special concentration on the hippocampus (Davis et al., 2005) for this specific reason.

Hippocampal sclerosis has been extensively studied (e.g., Walker, Chan, & Thom, 2007). For example, evidence suggests that sclerotic process is progressive (Bernasconi, Natsume & Bernasconi, 2005; Bernhard et al., 2009; Fuerst, Shah, Shah, & Watson, 2003; Sloviter, 2005) as seizures continue. The sclerotic process is characterized by cell loss (atrophy), most extensively in the dentate hilus and the CA1 region of the hippocampus. Cell loss is most common in excitatory neurons, whereas inhibitory neurons are more preserved (Engel et al., 2005). As the sclerosis progresses,

inhibitory neurons continue to sprout and innervate wider cortical areas (Babb, Pretorius, Mello, Mathern, & Levesque, 1992). This increased inhibition is related to "complex interactions among different neuronal groups," including spatially heterogenous activation of the medial temporal cortex and extra-temporal regions (Truccolo et al., 2011, p. 1), and in turn, heightened epileptogenicity. Once an area of seizure focus has been established, epileptic discharges in one area "may act to kindle distant structures" (Engel et al., 2005, p. 24), leading to generalized seizures (Jeffreys & Mellanby, 1998).

Hippocampal Sclerosis and Cognition

Individuals with TLE resulting from hippocampal sclerosis are at high risk for cognitive deficits (Dodrill, 2008; Jokeit, & Ebner, 2002), especially episodic memory deficits (Helmstaedter, 2005; Oddo et al., 2006). The medial temporal lobes (and the hippocampal formation in particular) are involved in the potentiation of recent and short-term memory into long-term memory (Patestas, & Gartner, 2006). Injury to this region of the brain is associated with problems learning new information as well as recalling previously learned information (Patestas, & Gartner, 2006).

The nature of memory impairment in hippocampal sclerosis is often a function of the lateralization of language in the individual with TLE (Goldstein, 1997). Although most individuals show left-hemispheric dominance for language (Blumenfeld, 2002), some individuals show a right-hemispheric dominance for these functions (Kolb, & Whishaw, 2009). In individuals for whom the epileptic focus is ipsilateral to most language processing, a deficit in memory for verbal material is common; in individuals whose epileptic focus is contralateral to language localization, memory deficits for visuospatial material are more common (Goldstein, 1991, 1997; Jokeit, & Ebner, 2002; Thompson, & Trimble, 1996).

Nociferous cortex. Importantly, the cognitive impairments associated with TLE and hippocampal sclerosis are not limited to memory. Individuals with TLE often show

deficits in a wide range of cognitive domains, such as attention, psychomotor speed, and EF (e.g., Dabbs, Jones, Seidenberg, & Hermann, 2009; Hermann et al., 2007; Hermann, Wyler, & Richey, 1988; Martin et al., 2005; Shulman, 2000; Silvia et al., 2003; Zhang et al., 2009). One possibility is that hippocampal sclerosis is associated with secondary cognitive deficits, especially executive dysfunction, due to the progressive nature of the condition and the impact of hippocampal sclerosis on function in other brain regions (e.g., Martin et al., 2000). This is a form of the *nociferous cortex hypothesis,* the idea that

> Epileptogenic cortex adversely affects the extra-temporal regions that mediate executive system abilities, thereby resulting in performance deficits.
> Hermann & Seidenberg, 1995, p. 809

The site of epileptic focus (e.g., temporal subcortex) is not only impaired in function, but also may impair the function of other areas of the brain (Devinsky, 2005). Sclerotic tissue in the temporal lobe has a radiating effect, negatively affecting remote areas of cortex (Martin et al., 2000; Seidenberg et al., 1998). This may, in turn, cause multiple cognitive deficits through remote structural-functional associations.

In their early speculation about what might underlie the nociferous cortex hypothesis, Hermann and Seidenberg (1995) suggested that hippocampal sclerosis might negatively affect function in other areas of the brain by injecting 'neural noise' (p. 816) and/or by generating abnormalities in metabolism and perfusion of those areas. Hippocampal sclerosis may be associated with either a functional or structural lesion to a distal area of cortex. For example, sclerotic hippocampi may inhibit function in networks within extra-hippocampal tissue. The ability of hippocampal lesions to inhibit function in distal areas has been demonstrated in humans, non-human primates, and rats (Squire, 1992; Stark, 2007; Zola-Morgan, Squire, & Amaral, 1986; Zola-Morgan, Squire, Amaral, & Suzuki, 1989).

More recent studies have raised the possibility of structural changes in remote areas as a result of hippocampal sclerosis (see Keller & Roberts, 2008, for a review). Dabbs et al. (2009) investigated the relationship between hippocampal sclerosis and other neuroanatomical structures. MRI data from individuals with medically refractory TLE were compared with MRI data from normal controls. Results showed that the extent of medial temporal (hippocampal) atrophy was associated with diverse neuroanatomical changes, which were in turn related to impaired memory, disrupted EF, and slowed psychomotor speed. For example, hippocampal sclerosis was positively associated with bilateral reductions in cortical thickness. Individuals with hippocampal atrophy and reduced cortical volume also showed reduced subcortical and cerebellar volume. These neurological changes extended beyond the epileptogenic hippocampus and affected both temporal and extra-temporal regions, ipsilateral and contralateral to the side of seizure onset. Dabbs and his colleagues concluded that degrees of cognitive impairment are associated with this pattern of neuroanatomical abnormalities in a "generally stepwise" (p. 445) fashion. Individuals with the most abnormalities in cortical, subcortical, and cerebellar structures showed the greatest impairment on measures of memory, psychomotor speed, and EF (Dabbs et al., 2009).

Similar to the results of Dabb et al., (2009), several recent publications from the Montreal Neurological Institute have also shown distal cortical atrophy associated with hippocampal sclerosis (Bernasconi, Concha, & Bernasconi, 2010; Bernhardt et al., 2008; Bernhardt et al., 2009). Using MRI to assess cortical volume, Berhardt et al. (2008) found several areas of thinning in both left- and right-sided TLE patients. Cortical thinning was observed in bilateral superior, middle, and medial frontal gyri, the precentral gyrus, the paracentral lobule, and the bilateral cingulate and contralateral occipito-temporal regions. The authors report that among left-sided TLE patients, "the most severe frontal thinning occurred in ipsilateral precentral regions with an absolute

decrease of more than 0.3mm^3 (corresponding to *>10% decrease in cortical thickness*)" (p. 518, italics added). They observed a similar pattern among right-sided TLE patients, although they noted that the atrophy in these patients was "less widespread" (p. 518).

In a longitudinal follow-up study, Bernhardt et al. (2009) examined progression of cortical atrophy in patients with refractory TLE. Advancing cortical atrophy was found both ipsilateral and contralateral to seizure onset. Notably, the rate of bilateral PFC atrophy exceeded 0.05mm^3 each year, as the disease progressed. Bernhardt et al., (2009) found that the duration of illness was associated with how quickly atrophy progressed: specifically, in patients with more than 14 years of refractory TLE, ipsilateral and contralateral cortical atrophy progressed faster than in individuals with fewer years of illness. A more recent study (Bernhardt et al., 2010) found similar results for TLE patients with hippocampal sclerosis, leading the authors to conclude "there is overall agreement on widespread frontolimbic atrophy in [TLE with hippocampal sclerosis]" (p. 1781).

Indeed, there is converging evidence to support the association between hippocampal sclerosis and distal cortical atrophy. Using a voxel-based morphometry (VBM) MRI protocol, Lin and his colleagues (2007) examined global cortical thickness in patients with refractory TLE. Both left- and right-sided TLE patients showed up to 30% volume decrease in bilateral frontal, temporal and occipital cortex, relative to healthy controls. Similar to the results of Bernhard et al. (2009), Lin and colleagues (2007) also found a significant negative correlation between duration of illness and cortical volume in the superior frontal cortex ipsilateral to seizure onset.

Functional neuroimaging has demonstrated that individuals with medically refractory TLE show reduced functional connections between sclerotic hippocampi and distal areas of cortex, including the PFC. Using a BOLD fMRI protocol, Frings, Sculze-Bonhage, Spreer, and Wagner (2009) compared the functional connectivity between

hippocampi and other cortical areas of a control group and a group of individuals with refractory TLE. The researchers found that individuals with TLE showed disrupted functional connectivity between epileptogenic hippocampi and the temporal gyrus, amygdala, and PFC. Specifically, data showed that when TLE patients had unilateral left hippocampal sclerosis, functional activation of the medial temporal/PFC network was particularly decreased.

In a similar vein, MRI research from the University of Liverpool showed that individuals with refractory TLE experience bilateral dorsal PFC atrophy as well as hippocampal atrophy ipsilateral to seizure onset (Keller, Baker, Downes, & Roberts, 2009). Keller and his colleagues (2009) examined hippocampal, dorsal and ventral PFC, and cerebral hemisphere volume(s), as well as patient performance on a number of neuropsychological tests, including measures of EF. Results showed that hippocampal volume was reduced only ipsilateral to site of seizure onset. In both individuals with left- and right-sided TLE, there was no reduction in ventral PFC volume when compared to controls. Right dorsal PFC volume was reduced in both individuals with left and right TLE, with “a possible trend in the left DPFC” (p. 190) as well.

Keller et al. (2009) also examined patient performance on the Stroop test, a letter fluency task, and two working memory tasks-- the Letter Number Sequencing and Spatial Span subtests from the Wechsler Memory Scale - III. Patients with left- and right-sided TLE performed similarly on the Stroop and working memory tasks, but those with left-sided TLE (e.g., those with reductions in left hippocampal volume) performed more poorly on the letter fluency task. When data from both left- and right-sided TLE patients were combined, there was a positive correlation between Wechsler Memory Scale working memory tasks and several neuroanatomical areas: left dorsal PFC volume, bilateral PFC volume, whole (dorsalal and ventral) left PFC volume, and whole right PFC volume (Keller et al., 2009). There were no significant correlations between

hippocampal volume and measures of working memory. Performance on the letter fluency task was positively correlated with left hippocampal volume, left dorsal PFC volume, and total left PFC volume. Patient performance on the Stroop task was positively correlated with left ventral PFC volume alone.

Notably, when patients with right-sided TLE were examined separately, several other significant correlations emerged. Working memory was positively correlated with left ventral PFC volume, whole right PFC volume, and total bilateral PFC volume. Verbal fluency was positively correlated with the left dorsalateral PFC and total right PFC volume. Finally, Stroop test performance was positively correlated with left ventral PFC volume. No significant neuroanatomic-EF correlations were found for the left-sided TLE patients. The authors conclude that "aberrant hippocampal-fronto-striatal neurophysiological processes account for at least part of the executive dysfunction found in patients with TLE" (Keller et al., 2009, p.194).

Hippocampal involvement in EF. Importantly, the degree of hippocampal sclerosis itself is positively correlated with cognitive deficits. Evidence from anterior temporal lobectomy patients suggests that, as sclerosis progresses, memory worsens, as does EF (Bell & Davies, 1998; Frodl et al., 2006; Hermann, Wyler, & Richey, 1988; Jokeit et al., 1997; Kent et al., 2006). In contrast with the nociferous cortex hypothesis, some have posited that the hippocampus itself plays an active, direct role in diverse cognitive functions, including aspects of EF such as updating (e.g., Corcoran & Upton, 1993; Wall & Messier, 2001; see also Frodl et al., 2006). Consequently, the reasoning follows, EF deficits in medically refractory TLE stem directly from abnormalities in the structure and function of the hippocampus rather than indirectly from the effect of hippocampal lesions on other brain regions. Hermann and Seidenberg (1995) refer to this as the *hippocampal hypothesis.*

Direct involvement of the hippocampus in EF is not uncontested. Some studies have found significant relationships between hippocampal volume and EF tasks in normally aging individuals (Oosterman et al., 2008), as well as in individuals with TLE (e.g., Corcoran & Upton, 1993; Giovagnoli, 2001) and other types of neuropathology (Szeszko et al., 2002). Others have not (e.g., Gunning-Dixon & Raz, 2003; Nestor et al., 1993). Some of the positive findings come from studies that report an association between the combined volume of the anterior and posterior regions of the hippocampus and some aspects of EF (Corcoran & Upton, 1993; Giovagnoli, 2001; Keller et al., 2009). Giovagnoli compared the performance of individuals with TLE and frontal lobe epilepsy on select EF tasks. Individuals with left-sided TLE (and left hippocampal sclerosis) showed a pattern of impairment similar to people with left frontal epilepsy on EF tasks. Specifically, individuals with left hippocampal sclerosis showed impaired sorting ability and more perseverative errors on a Modified WCST than did controls (Giovagnoli, 2001), reflecting a weakness in the ability to shift between categories. Giovagnoli concluded that left hippocampal lesions may "*determine* significant impairment of sorting ability" (p. 148; emphasis added) in individuals with TLE. Similarly, Keller and his colleagues found that left hippocampal atrophy subsequent to sclerosis was associated with decreased letter (verbal) fluency, which is thought to measure mental flexibility and inhibition in addition to semantic memory retrieval (Ylikoski & Hanninen, 2003; Strauss et al., 2006).

Szeszko and his colleagues attribute these different findings to the "distinct neuroanatomical and functional differences between posterior and anterior hippocampal entorhinal-hippocampal projections" (2002; pp. 217-218). They argue that dysfunction in the anterior hippocampus (but not the posterior hippocampus) is associated with disruption in the medial frontolimbic system, and consequent deficits on EF tasks. Szeszko et al. (2002) emphasize the importance of anterior and posterior hippocampal connections with other areas of subcortex: the anterior portion of the hippocampus

receives many afferent projects from the striatum and limbic system, while the posterior portion of the hippocampus receives many afferent projections from posterior areas of cortex. When they examined a group of men experiencing a first-onset schizophrenic episode, Szeszko et al. (2002) found that bilateral anterior hippocampal volume was significantly correlated with several EF tasks (e.g., the Trail Making Test Part B, the WCST, and the WAIS-R Picture Arrangement subtest), as well as motor functioning. No such relationship between posterior hippocampal volume and cognitive performance was found. The strength of the relationship between anterior hippocampal volume and EF was in fact stronger than the relationship between anterior hippocampal volume and either language or memory (Szeszko et al., 2002). Interestingly, this relationship was not found for women in the same study.

Neural network models (which mathematically model the synchronicity of activation in specific neural areas [Arbib, 2003]) also lend support to the involvement of the hippocampus in cognitive shifting, updating, and inhibiting. For example, in their computational model, Banquet, Burnod, Gaussier, Quoy, and Revel (2004) investigated the role of the hippocampus in updating and goal-oriented behaviour. Their model posits that the hippocampus projects spatial representations of goal salient locations to the PFC, which enables

> Top down-output from the PFC and the bottom-up output from the hippocampus [to] combine onto the [nucleus] accumbens, the first stage for the stepwise selection and implementation of the optimal actions [to reach] the goal. Banquet et al., 2004, p. 1499

Another computational network emphasizes the impact of hippocampal circuits in memory-guided, goal-directed behaviour (Hasselmo, 2004). In this model, involvement of the hippocampus in episodic memory retrieval enables selection of appropriate goal-directed behaviours by the PFC (Hasselmo, 2004). Along with demonstrating the role of

the hippocampus in goal-directed behaviour, these studies may also be said to reflect the role of the hippocampus in spatial learning.

Turnock and Becker (2008) proposed a computational model wherein the hippocampus influences goal-directed behaviour by suppressing PFC synaptic input to the nucleus accumbens. Experimental computer simulation of the model suggested that these hippocampal-PFC interactions enabled environmental cues to inhibit automatic responses, thereby allowing "flexible selection of previously learned associations and behaviours" (Turnock, & Becker, 2008, p. 87). All three of these computational models (Banquet et al., 2004; Hasselmo, 2004; Turnockm & Becker, 2008) provide mathematical support for the direct involvement of the hippocampus in goal-directed behaviour, an aspect of EF.

Others reject the hippocampal hypothesis, instead emphasizing the role of distal, secondary cognitive deficits in executive dysfunction in individuals with TLE. That cognitive deficits may be secondary effects of remote epileptic cortex was initially proposed in the mid 1950s by neurologists Penfield and Jasper, who had observed that a child's behaviour improved significantly after surgical resection of his epileptic focus (Devinsky, 2005). In the years that followed, other patients showed post-surgical improvement in cognitive functioning supported by neuroanatomical areas remote from the resected diseased epileptic tissue. These data were seen as providing support for the nociferous cortex hypothesis (Devinsky, 2005; Mayanagi, Watanabe, Nagahori, & Nankai, 2001).

Nociferous cortex and hippocampal sclerosis. In 1995, Hermann and Seidenberg considered patient performance on EF tasks in light of the hippocampal and nociferous cortex hypotheses. They suggested that if the hippocampal hypothesis were true, surgical resection of a hippocampus without sclerosis in TLE patients would produce a decline in EF after operation while resection of a sclerotic hippocampus

should not result in a drop in EF. Contrary to the predictions based on the hippocampal hypothesis, Hermann & Seidenberg (1995) found no relationship between degree of hippocampal sclerosis and EF. They concluded that the EF deficits in TLE patients must be due to secondary effects of the sclerosis, consistent with the nociferous cortex hypothesis. In particular, they suggested that sclerotic hippocampi in individuals with TLE had a nociferous, irradiating effect on distal brain areas, and specifically on the frontal cortex.

Seidenberg et al. (1998) extended their research by examining neuropsychological data from patients who had been assessed both *before* and *after* the removal of sclerotic hippocampi. Data from these patients indicated that EF scores were similarly poor at both assessments. Seidenberg and Hermann posited that if hippocampal sclerosis was directly associated with EF deficits, then subsequent to removal of the sclerotic tissue performance on EF tests should have improved. When executive functions remained equally poor after hippocampal resection, Seidenberg et al. (1998) saw the results as strongly supportive of the nociferous cortex hypothesis.

Importantly, direct involvement of the hippocampus in EF does not preclude secondary cognitive deficits in distal areas of tissue. The EF deficits observed in individuals with TLE may result from both nociferous effects on remote cortex as well as direct involvement of the hippocampus in EF. Recall that individuals with hippocampal sclerosis also show deceased neocortical and subcortical thickness, decreased corpus callosi, and reduced cerebellar gray matter (Dabbs et al., 2009). Individuals who are the most cognitively impaired (e.g., impaired across multiple domains including EF, memory, and psychomotor speed) show a distinct neuroanatomical profile including both temporal and extratemporal abnormalities (i.e., atrophy). These results suggest that the longer seizures are not fully controlled, hippocampal sclerosis, as well as structural

abnormalities in other areas of the brain, may increase along with concomitant behavioral impairment.

In support of this, recent neuroimaging data suggest that hippocampal sclerosis together with atrophy in other cortical areas, including the PFC, may be associated with cognitive deficits. Hermann et al. (2003) found that patients with medically refractory TLE had significantly reduced cortical volume, as well as diminished total cerebral tissue. Notably, these reductions were apparent in the frontal cortex. Data from patients with other neurological diseases, such as Parkinson's disease (Bruck, Kurki, Kaasinen, Vahlberg, & Rinne, 2004) and schizophrenia (Breier et al., 1992; Seidman et al., 2002) have also shown a correlation between hippocampal sclerosis and PFC atrophy.

Executive Functioning, PFC, and Hippocampal Sclerosis

A number of studies have been published about the extratemporal cognitive deficits associated with hippocampal sclerosis and TLE. Numerous investigators have reported that individuals with TLE show impairments in EF (e.g., Dodrill, 1978, 1986; Hermann, & Seidenberg, 1995; Martin et al., 2000; Seidenberg et al., 1998; Silvia et al., 2003). Recall that while EF may be diffusely localized, the PFC plays an important role in these functions. Hermann and colleagues (1988) found that approximately 50% of their patients with TLE performed in the clinically impaired range on the WCST. Hermann and colleagues (1991) found that approximately one third of their patients with TLE showed deficits in EF similar to those of frontal lobe patients. N'Kaoua and colleagues (2001) found that patients who had a temporal epileptic focus in either hemisphere were impaired on a task of semantic fluency, considered a measure of EF.

Review of recent studies that have examined EF deficits in patients with hippocampal sclerosis and TLE helps illustrate the importance of further study in this area. For example, Labudda et al. (2009) assessed decision-making ability in patients with medically refractory TLE, and compared their decision-making abilities to control

participants. Data showed that individuals with refractory TLE showed serious impairments not only on the Iowa Gambling task, but also on a group of more traditional neuropsychological tests of EF (e.g., the Colour-Word Interference [Stroop] Task; Labudda et al., 2009). Labudda (2009) and her colleagues concluded that medial temporal sclerosis, and specifically hippocampal sclerosis, can cause impairments in decision making and executive functioning.

In a similar study, Schacher and her colleagues (2006) looked at whether refractory TLE is related to deficits in advanced social cognition. Schacher et al. compared TLE patients with hippocampal sclerosis, epilepsy patients without hippocampal sclerosis, and healthy control participants on a test requiring recognition of social faux-pas. Data showed that individuals with hippocampal sclerosis were significantly less likely to recognize a faux-pas than their peers in either group. These results are especially meaningful as Schacher et al. controlled for reading and language dysfunction in their analyses. The authors postulated that hippocampal sclerosis affects higher-order aspects of social cognition through the secondary effects on lateral temporal, frontal, and other cortical structures (Schacher et al., 2006).

Critically, although both hippocampal and nociferous cortex hypotheses have been examined by investigating hippocampal sclerosis and EF, only one study has directly examined the individual effects of hippocampal sclerosis *and* prefrontal atrophy on EF in patients with medial temporal lobe epilepsy. Keller et al. (2009) found that left hippocampal volume was positively correlated with performance on a verbal fluency task, as well as with prefrontal volume, but did not investigate the *combined* effects of hippocampal sclerosis and PFC atrophy on EF. Hermann & Seidenberg's (1995) study examined only the relationship between hippocampal sclerosis and disruption of EF, but did not consider PFC volume. When no relationship was found between hippocampal sclerosis and EF, Hermann and Seidenberg suggested that secondary physiological

disruption to areas of frontal cortex was involved in lowering performance on measures of executive function in patients with hippocampal sclerosis. Consequently, it was important to continue the objective investigation of the role of *both* hippocampal sclerosis *and* PFC volume in EF deficits. It may well be that hippocampal sclerosis and reduced PFC volume are common independent endpoints of medically refractory TLE, the result of a disrupted PFC-medial temporal neural network. The present study examined whether hippocampal sclerosis and reduced PFC volume, in some combination, were associated with EF deficits.

Structural Neuroimaging of Hippocampal Sclerosis and PFC Volume

While MRI is often used to examine hippocampal abnormalities patients with TLE, MRI can also be used to calculate cortical grey, as well as white matter volume. As previously discussed, neocortical and cerebellar volume decreases in patients with TLE as cognitive deficits worsen (Dabbs et al., 2009). Using VBM, Coan and colleagues (2009) found progressive white and gray matter atrophy in patients with hippocampal sclerosis Higher seizure frequencies, as well as time since diagnosis, were also positively correlated with atrophy in the temporal and bilateral frontal regions (Coan et al., 2009). A benefit of using structural neuroimaging is the ability to compare and contrast neurobehavioral correlates of PFC volume as well as hippocampal sclerosis, and assess their relationship to EF deficits. If hippocampal sclerosis and reduced PFC volume are endpoints of the same epileptic process (as the data from Bernhardt et al., 2008; Bernhardt et al., 2009; Coan et al., 2009; Dabbs et al., 2009; and Lin et al., 2007 suggest), we may expect to see a relationship between the two and EF deficits. It will also be possible to investigate whether hippocampal sclerosis and PFC atrophy interact to produce these deficits.

Current Research

This study sought to investigate the roles of hippocampal sclerosis and PFC volume in producing executive functioning deficits in individuals with medically refractory TLE. Results allowed for evaluation of the hippocampal and nociferous cortex hypotheses, and specifically, enabled examination of the association between neuropathology in the medial temporal lobe and PFC volume in medically refractory TLE. Structural MRI and neuropsychological data from patients with medically refractory medial TLE were examined to investigate the relationship between hippocampal sclerosis, reduced PFC volume, and EF in these patients. In this context, the following issues were examined:

1. *The presence and extent of EF impairments, as measured by standardized neuropsychological measures, in individuals with medically refractory TLE.* Based on the research reviewed above, I hypothesized that individuals with medically refractory TLE would show impairment (relative to an appropriate normative group) across the following EF measures: the WCST Perseverative Error (PE) *T* score, the Trail Making Test Part B *T* score, the Digit Span subtest age scaled score from the WAIS-R, the California Verbal Learning Test (CVLT) Long Delay Yes/No Recognition Discriminability *z* score, letter and semantic fluency total correct *z* scores, as well as letter and semantic fluency switching *z* scores.

2. *The relationship between PFC volume and EF in individuals with medically refractory TLE.* Extensive research has linked the PFC to EF tasks. I hypothesized that bilateral PFC volume would be positively correlated with performance on EF test scores reflecting cognitive shifting, updating, and inhibiting.

3. *The association between hippocampal sclerosis and bilateral PFC volume in individuals with medically refractory TLE.* Previous reports indicate that, as hippocampal sclerosis worsens, there is simultaneous, progressive atrophy in extratemporal regions (e.g., Bernhardt, Worsley, Besson, et al., 2008; Bernhardt, Worsley, Kim, et al., 2009;

Coan et al., 2009; Dabbs et al., 2009; Lin et al., 2007), including the PFC (Keller et al., 2009). I hypothesized that hippocampal volume ipsilateral to seizure onset would be positively correlated with bilateral PFC volume in individuals with medically refractory TLE.

4. *The relationships among hippocampal volume, PFC volume, and EF.* Given the predictions above, I further hypothesized that after controlling for age and education, hippocampal sclerosis and bilateral PFC volume would each add predictive value to a linear model predicting performance on measures of EF in people with medically refractory TLE. Specifically, I expected to find evidence in support of both the hippocampal and nociferous cortex hypotheses.

Given the nature of the MRI data in the current study (structural), examination of the nociferous cortex hypothesis was limited to investigating structural changes, rather than functional lesions, to the PFC. In order to examine the nociferous cortex hypothesis, I examined whether bilateral PFC volume mediated the effect of hippocampal volume ipsilateral to seizure onset on EF deficits (Holmbeck, 1997). The nociferous cortex hypothesis would be supported if bilateral PFC volume mediated the relationship between hippocampal volume and EF. In order to examine the hippocampal hypothesis, I determined the relationship between hippocampal volume on the side of seizure onset and EF after statistically controlling for the association between bilateral PFC volume and EF. The hippocampal hypothesis would be supported if hippocampal volume on the side of seizure onset significantly predicted EF even after controlling statistically for the association between bilateral prefrontal volume and EF.

It was necessary to control for the recognized effects of age and education on EF performance (Rhodes, 2004) as these had the potential to obscure the relationships among hippocampal volume on the side of seizure onset, bilateral PFC volume, and EF.

5. *The performance of individuals with medically refractory TLE in other cognitive domains.* Consistent with the work of Hermann, Seidenberg, and colleagues (e.g., Dabbs et al., 2009; Hermann et al., 2003; Hermann et al., 2007; Oyegbile et al., 2004) I hypothesized that hippocampal sclerosis on the side of seizure onset and bilateral PFC volume would be more strongly predictive of performance on standardized tests of verbal memory, EF, and psychomotor speed than of performance on tests of visuoperceptual abilities, confrontation naming, and global intellectual function.

CHAPTER 2

Method

Participants

Data from 38 patients (22 female) with a history of early onset, medically refractory medial TLE and hippocampal sclerosis were used in this study. Patients were seen through the Epilepsy Program at the Wayne State University (WSU) School of Medicine. Selection criteria were modeled on the work of Hermann & Seidenberg (e.g., Oyegbile et al., 2004) and included (a) a chronological age between 18 and 65 years; (b) Full Scale IQ ≥ 69 as measured with the Wechsler Intelligence Scale(s); (c) adequate effort on neuropsychological measures as assessed by tests sensitive to response bias; (d) "MRI-measured unilateral hippocampal sclerosis and no other neuropathological lesion (on MRI or otherwise)" (C.R. Watson, personal communication, September 20, 2011).; and (e) no other neurological disorder.

Patients ranged in age from 18 to 65 (*M* = 34.7, *SD* = 11.8). Twenty-six patients (68%) were identified as Caucasian (non-Hispanic), eight (21%) as African American, one (3%) as Arabic, and ethnocultural data was not available for three patients (8%). Average length of illness was 22.4 years (*SD* = 14.4), and average age of seizure onset was 12.9 years (*SD* = 14.6). The mean number of anti-epileptic medications taken at the time of assessment ranged from one to five (*M* = 2, *SD* = 0.8). Table 1 lists the medications patients were taking at the time of neuropsychological assessment. Of the thirty-eight patients, two had been diagnosed with hypertension, one with diabetes mellitus, one with high cholesterol, one with heart disease, and three with asthma. With respect to psychiatric comorbidities, 14 patients (37%) indicated that they had been diagnosed with clinical depression, two (5%) with "other" mental health problems, and one patient (2%) reported a history of suicide attempts. Eighteen patients (47%) showed

Table 1

Anti-Epileptic Drugs Reported by Patients in Sample

Trade Name	Generic Name
Neurontin	Gabapentin
Leveiracetam	Keppra
Klonipin	Clonazepam
Lamictal	Lamotrigine
Depakote	Valproic Acid
Tegretol	Carbamazepine
Lacosamide	Vimpat
Topiramate	Topamax
Tempesta	Lorazepam

clinically elevated negative mood symptoms on clinical questionnaires (Minnesota Multiphasic Personality Inventory-2 [MMPI-2] or the Beck Depression Inventory [BDI]; see below). At the time of neuropsychological assessment, six of the patients used tobacco regularly, four patients reported occasional consumption of alcohol, and one patient indicated that he used illegal drugs.

Seventeen patients showed left (unilateral) hippocampal sclerosis, and 21 patients showed right (unilateral) hippocampal sclerosis. The modal number of years of education was 12 (M = 13.2, SD = 2.3), and there was no significant difference in education between patients with left versus right hippocampal sclerosis ($t[34]$ = 0.23, *ns;* two-tailed). Similarly, there was no difference in length of illness between left- and right-sided patients ($t[32]$ = 1.5, *ns;* two-tailed).

MRI scans from a control group of 55 (26 female) neurologically normal individuals were also included in MRI analyses to "normalize" volume measurements (Watson, Jack, & Cendes, 1997, p. 1523). This control group has been used to normalize hippocampal volume in the same patient sample in several previously published studies (e.g., Fuerst, Shah, Shah, & Watson, 2003; Watson, Cendes, Fuerst et al., 1997; Watson, & Williamson, 1994). The normalization process entails two steps. First, the mean total intracranial volume (TIV) of the control group is calculated. Second, the specific neuroanatomical region of interest (ROI) is normalized using the equation:

$$ROI_n = (TIV_c * ROI_p) / TIV_p. \quad (1)$$

Here ROI_n represents the normalized ROI for a given patient, TIV_c represents the mean TIV of the control group, and ROI_p and TIV_p represent that patient's ROI and TIV, respectively. The same normative control TIV value was used to normalize all MRI volumetric measurements in the present study.

This mathematical adjustment is made to allow meaningful comparison among patient and control group volumes, and to help correct for sex and head size (Watson,

Jack, & Cendes, 1997). The control group ranged in age from 8 to 85 (*M* = 49.8, *SD* = 23.5). Individuals in the control group were recruited for participation when they underwent MRI for another medical cause, and they received no remuneration. The control group data were collected in the mid-1990s at the Detroit Medical Center in Detroit, Michigan. Informed consent was obtained for all control individuals. No other information about the control group (e.g., IQ, education, ethnocultural data) was available, and thus it was not possible to describe this group on other variables or to compare the demographic characteristics of the control group to the patients with TLE.

In addition to the normalization of patient ROIs using the control group TIV data, ROIs were also transformed into a ratio score, using each patient's unique TIV:

$$ROI_{ratio} = ROI_p/TIV_{p.} \quad (2)$$

Here ROI_{ratio} represents the ratio score of a particular patient's ROI, and and ROI_p and TIV_p represent that patient's ROI and TIV, respectively. Statistical analyses were run using both the normalized ROI data and the ROI ratio scores. The results were comparable, and therefore only analyses using the normalized ROI data are presented in the Results section, below.

Neuropsychological Measures

Patients were administered a battery of neuropsychological tests that included a measure of intelligence (Wechsler Adult Intelligence Scale – Revised; WAIS—R; Wechsler, 1981), measures of verbal and visual memory (Wechsler Memory Scale—Revised; WMS—R; Wechsler, 1987), as well as verbal list learning (CVLT, Delis, Kramer, Kaplan & Ober, 1987); measures of semantic and letter fluency (Animal Naming test [Tombaugh, Kozak, & Rees, 1999]; Multilingual Aphasia Exam Controlled Oral Word Association Subtest [Benton, Sivan, Hamsher, Varney, & Spreen, 1994]) as well as expressive and receptive language (Multilingual Aphasia Exam Visual Naming subtest and Token Test; Benton et al., 1994); and speeded psychomotor processing and divided

attention (Trail Making Test Parts A and B; Reitan & Wolfson, 1985). Academic achievement was assessed with the Wide Range Achievement Test—3 (Wilkinson, 1993). Visuospatial functioning was assessed using the Judgment of Line Orientation test (JOLO; Benton et al., 1994) Bilateral sensation and motor dexterity were assessed with components of the Halstead-Reitan Neuropsychological Test Battery (e.g., Finger Tapping Test, Reitan-Klove Sensory-Perceptual Examination; Reitan & Wolfson, 1985). Response bias was assessed using the Test of Memory Malingering (TOMM; Tombaugh, 1996), as well as by comparing the difference between digit span forward and backward on the Digit Span subtest of the Wechsler Adult Intelligence Scale—Revised (Iverson, & Tulsky, 2003). Patients who completed an independent effort test (i.e., the TOMM) did so after the standardized neuropsychological battery was altered for the entire service in the late 1990s. EF was assessed using the WCST (Heaton et al., 1993), as well as several other measures (see below). Personality and psychopathology was assessed with either the MMPI-2 (Butcher, Dahlstrom, Graham, Tellegen, & Kraemmer, 1989) or the BDI (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961).

In addition to raw scores, adjusted *T* or *z* scores were calculated where possible to take into account demographic variables known to influence test performance, using normative data (see below for more detail). Table 2 includes the list of tests used in the analyses for this study.

EF measures. Several neuropsychological measures were used to assess EF. In addition to the WCST (Heaton et al., 1993), speeded alphanumeric sequencing (Trails B), components of the CVLT, verbal fluency tasks, and the Digit Span subtest from the Wechsler Adult Intelligence Scale – Revised were also used.

The WCST measures a number of performance related factors, for example, the number of cards sorted until the first category is completed, as well as the number of overall errors made. In summary, patients are instructed to "match" a response card to

Table 2

Neuropsychological Test Battery Given to Patients with Medically Refractory Temporal Lobe Epilepsy

Domain	Test	*N*
Intelligence	Wechsler Adult Intelligence Scale—Revised	34
Language	Semantic verbal fluency test	34
	Select Subtests from the Benton Multilingual Aphasia Exam	
	Visual Naming	32
	Token Test	33
	Controlled Oral Word Association Test	33
Visual perceptual	Judgment of Line Orientation Test	24
	Reitan-Klove Sensory-Perceptual Examination	34
Memory	California Verbal Learning Test	34
	Wechsler Memory Scale—Revised	35
Executive function	Wisconsin Card Sorting Test	34
Motor/Psychomotor speed	Halstead-Reitan Neuropsychological Test Battery	
	Grooved Pegboard Test	35
	Finger Tapping Test	34
	Grip Strength Test	34
	Trail Making Test Parts A and B	35
Academic Achievement	Wide Range Achievement Test—3	34
Effort	Test of Memory Malingering	3
Personality/Psychopathology	Minnesota Multiphasic Personality Inventory-2	31
	Beck Depression Inventory	3

one of four stimulus cards. Each stimulus card is unique in colour, number, and shape. The patient is instructed to place ("sort") each response card under one of the four stimulus cards. After each placement, the patient is told whether he or she has responded correctly or incorrectly. After correctly placing 10 cards according to the first matching criteria, the criteria shift and the patient must work out the new sorting strategy. This procedure is repeated until six full categories have been completed or until all 128 cards have been placed.

The WCST Perseverative Error (PE) score reflects the number of times an individual has continued to sort cards by repeating a specific response that the examiner has indicated is no longer correct. As such, it is thought to measure the ability to shift cognitive set (Konishi et al., 1999; Mullane & Corkum, 2007; Robbins, Weinberger, Taylor, & Morris, 1996). The more perseverative errors a patient makes, the poorer his or her performance. The number of perseverative errors was transformed into a *z* score using the normative data gathered by Heaton, Miller, Taylor, and Grant (2004), which are adjusted for age and education, but not ethnocultural status. A lower *z* score indicates poorer performance. Neuroimaging studies have repeatedly demonstrated PFC activation when individuals are engaged in the WCST (Haut et al., 1996; Lie, Specht, Marshall & Fink, 2006; Lombardi et al., 1999). In particular, patients with right PFC lesions have been found to make more perseverative errors than both normal controls and individuals with left PFC lesions (Stuss et al., 2000).

In the Trail Making Test Part B, patients are asked to draw a line connecting numbers and letters, in proper alphanumeric order, as quickly as possible. Total time required to complete the task, as well as total errors, is recorded. Because participants must correct any errors before proceeding with the test, the total time score indirectly reflects errors. When patients do not complete either Trails Part A or B within 300 seconds, the task is discontinued and the completion time is noted as 300 seconds.

Normative data gathered by Heaton, Grant, and Matthews (1991; adjusted for age, sex and education, but not ethnocultural status) were used to score the time required for completion of this task. Again, a lower *T* score indicates poorer performance.

The Trail Making Test Part B is widely recognized as a measure of set maintenance or the ability to shift between multiple stimuli (e.g., Burgess, Alderman, Evans, Emslie, & Wilson, 1998; Ylikos & Hanninen, 2003). Functional neuroimaging studies have implicated left PFC in the Trail Making Test (e.g., Moll, de Oliveira-Souza, Moll, Bramati, & Andreiulolo, 2002), as have studies using diffusion tensor imaging (DTI; Perry et al., 2009). Using DTI, Perry and her colleagues found that the integrity of white matter tracts connecting the PFC and "posterior association areas" (p. 2841) is associated with performance on Part B of the Trail Making Test.

The ratio of Trails B/Trails A (a numeric sequencing task) was also coded. The Trails B/A ratio may reflect a "purer measure" of the cognitive flexibility required by the task (Strauss et al., 2006, p. 657; Lamberty, Putnam, Chatle, Bieliauskas, & Adams, 1994). The guidelines presented by Lamberty et al. (1994) were used to classify the Trails B/Trails A ratio as either impaired or non-impaired. The Trails B/A ratio score was also transformed into a *z* score using the normative data of Tombaugh (Strauss et al., 2006), which adjust for age and education.

The number of errors made on Part B of the Trail Making Test was also coded. Stuss, Bisschop, and colleagues (2001) found that patients with frontal lesions took excessive time to complete Part B and made more errors compared to their peers with non-frontal lesions (Stuss et al., 2001). Stuss et al. (2001) suggest that error analysis in Trail Making Test Part B may be more sensitive to PFC function than total time required to complete the task. Specifically, the authors report that individuals who make more than one error on Part B of the test are significantly more likely than their peers to have frontal lobe dysfunction.

In the Digit Span subtest on the WAIS-R, patients are asked to repeat back a series of numbers, in either forward or reverse order, immediately after presentation. A patient's ability to repeat numbers in reverse order requires the updating of working memory and has been frequently used as a working memory task (e.g., Baddeley & Sala, 1996; Vallar & Papagno, 1995). Age-scaled scores were derived using the normative dataset from Wechsler (1981). These normative data do not correct for education or ethnocultural status. Lower age-scaled scores indicate poorer performance on this task. Both neuroimaging and transcranial stimulation studies have implicated bilateral PFC in both Digit Span Forward and Backward (Aleman & van't Wout, 2008; D'Esposito, Cooney, Gazzaley, Gibbs, & Postle, 2006).

The CVLT was also used in this study. The CVLT is a word learning, verbal memory task. In the first part of the task, patients are asked to learn a list of words (list A). After five learning trials for list A, patients are asked to learn a second (interference) list (list B). The Long Delay subtest is administered approximately 20 minutes later. In this task, patients are asked to repeat back as many words as they can from list A, leaving out any words from list B. Following this, they are presented with a longer list of words, containing words from list A, list B, and new words. Patients are asked to identify which of the words from this longer list were among list A. Patients are required to ignore all words that were not on list A. The number of correct hits versus false positive responses is transformed into the CVLT Long Delay Yes-No Recognition Discriminability score. The discriminability score is calculated by examining the standard deviation units between a patient's correct responses and false positive responses. Delis et al. (2005) report that the discriminability score is "analogous to a contrast *z* score" (p. 710). A discriminability score of 0 means that the patient was unable to distinguish between words from list A and non-list A words. These CVLT scores were transformed to z

scores using normative data corrected for age and gender, but not ethnocultural status (Fridlund & Delis, 1987).

While the CVLT is considered primarily to be a memory test, others have also noted that certain subtests (the Long Delay Yes/No Recognition Discriminability subtest in particular) require cognitive inhibition (see Baldo, Delis, Kramer, & Shimamura, 2002). Individuals with frontal lobe lesions have poorer CVLT Long Delay Yes/No Recognition discriminability scores, as well as poorer overall recall, and make more intrusions than do normal, healthy controls (Baldo et al., 2002). The authors write that these results may reflect the role of the PFC in "inhibition of irrelevant activations" (p. 545). Functional neuroimaging has shown activation of both the right PFC and right anterior hippocampus in the Long Delay Yes/No Recognition Discriminability component of the CVLT (Johnson, Saykin, Flashman, McAllister, & Sparling, 2001).

Verbal fluency tasks require patients to generate as many words as they can, beginning either with a specific letter (letter fluency) or belonging to a specific semantic category (semantic fluency, Animal Naming) over a short time period. The COWA is a letter fluency test, in which patients are given three trials, using a new letter each time. In the semantic fluency task, patients are given 60 seconds to name as many animals as they are able, regardless of the letter the animal starts with. To score the COWA, the correct responses made across the three trials of letter fluency are summed, then corrected for age and education. The corrected scores are then compared to data from normal control subjects (Benton et al., 1994), and coded as a percentile score. Lower percentile scores reflect poorer performance. The COWA normative data are not adjusted for ethnocultural status. To score the semantic fluency task, the total number of correct responses is transformed into a *z* score using data from normal controls (Tombaugh et al, 1999), which are also corrected for age and education.

Qualitative performance (e.g., switching between clusters of semantically and phonetically similar words) on these tasks was also examined, using the protocol outlined by Troyer, Moscovitch, and Winocur (1997). Clustering refers to the generation of two or more adjacent words within the same subcategory (Troyer et al, 1997). The total number of switches was coded for both semantic and letter fluency tasks. Switching occurs when the individual begins to generate words that belong to a different subcategory. As per Troyer et al.'s scoring guidelines, the total number of switches made was calculated by summing the number of transitions between clusters across the three letter fluency trials or single semantic fluency trials. When calculating number of switches, errors and repetitions are included (see Troyer et al., [1997] for more information on scoring guidelines). Data were first corrected for age and education using the protocol outlined by Troyer (2000), and switching scores were then transformed into *z* scores using data from normal controls (Troyer, 2000).

Troyer and her colleagues (1997) have proposed that mean cluster size is associated with temporal lobe activation, while the number of switches is associated with frontal lobe activation. Subsequent lesion studies have shown that an abnormally low mean cluster size is usually associated with disruptions in temporal cortex function, while an abnormally low number of switches is associated with disruptions in PFC and medial frontal cortex function (see Strauss et al., 2006, for a brief review).

Definition and computation of EF indices. In order to assess inhibiting, the WCST PE *T* score was used. Cognitive shifting was assessed using the Trails B/A ratio *z* score. Updating was assessed using the Digit Span age-scaled score from the WAIS-R. In addition to independently assessing inhibition, cognitive shifting, and updating, hypotheses 1 and 2 were evaluated by combining the EF scores listed above into an overall EF composite *z* score. The Trail Making Test Part B *T* score, Trail Making Test B/A ratio *z* score, the letter fluency percentile score, semantic fluency *z* score, letter and

semantic fluency switching *z* scores, CVLT Long Delay Yes-No Recognition Discriminability *z* score, Digit Span age-scaled score, and the WCST PE *T* score were combined to create an overall EF composite *z* score.

To do this, the WCST PE *T* score, Trail Making Test Part B *T* score, Digit Span subtest age-scaled score, and letter fluency percentile score were converted into standardized *z* scores. These were summed with the CVLT Long Delay Yes-No Discriminability *z* score, Trails B/A ratio *z* score, semantic fluency *z* score, as well as letter and semantic fluency switching *z* scores (see Table 4), and averaged to create an overall EF composite *z* score. This overall EF composite *z* score was prorated in cases of missing data. This standardized composite *z* score was used as an overall indicator of performance on EF measures.

Imaging Measurement and Processing

MRI scan acquisition. MRI studies were performed using the units at Harper University Hospital and Children's Hospital, both in Detroit, MI. Scans were made using a 1.5T magnet 1.5-3 millimeter thick slices, and spoiled gradient echo sequences (SPGR). See Watson & Williamson (1994) for more information on this MRI protocol.

MRI scan analysis. ***Hippocampal Volume****.* Volumetric measurements of bilateral hippocampi were made by Dr. Craig Watson, using the method outlined by Watson, Cendes, Fuerst et al. (1997). Volumetric analysis is a reliable way to assess extent of hippocampal sclerosis, as increased sclerosis results in reduced hippocampal volume. The contours of the hippocampi were identified entirely with a manual contouring function. Slice volume was then calculated by summing the area outlined by slice thickness. Total hippocampal volume was calculated by summing slice volumes. Total intracranial volume was calculated in the same way. Hippocampal volume was then corrected for total intracranial volume, providing a sum in millimeters cubed. Bilateral hippocampal measurements were made, regardless of side of seizure onset.

This allowed for comparison of the hippocampal atrophy on the epileptogenic side to the contralateral hippocampus. Given the limitations of the volumetric software, it was not possible to separate the hippocampus into distinct neuroanatomical areas (e.g., anterior, posterior) in this analysis.

Bilateral PFC Volume. There is some variability in how the PFC has been defined in previous studies: for example, some studies focus specifically on the dorsolateral PFC, Brodmann's areas 9 and 46 (e.g., Bonillha et al., 2008; Petrides, & Pandya, 1999; Zuffante et al., 2001). Other studies have used Brodmann's areas 9, 10, 11, and parts of 46 in their designation of the PFC (e.g., Hirayashu et al., 2001; Wible, Shenton, Fischer, et al., 1997; Wible, Shenton, Hokama et al., 1995). For the purposes of this project, PFC was defined as Brodmann's areas 9, 10, 11, and the anterior portion of 46 (Pandya & Yeterian, 1990).

PFC volume was assessed using a system similar to that involved in hippocampal measurement. After training in the appropriate use of the volumetric software for PFC analysis by Dr. Craig Watson, I made bilateral PFC measurements. Seven neurologically normal individuals were included in the PFC volumetric measurements, and I made PFC volumetric measurements blind to each individual's neurological (TLE patient or individual from the control group) and neuropsychological status. Again, given the limitations of the software, it was not possible to separate the PFC into distinct neuroanatomical areas for this analysis. Gray and white matter volumes were summed separately, calculated by summing individual slices across a set of scans. Contours of the PFC were identified with a manual contouring function, measured anteriorly from the first slice containing brain tissue, and continuing up to the slice immediately anterior to the corpus callosum. The average number of slices analyzed for measurement of PFC volume was approximately 25 per patient. It took roughly 30 minutes to complete the manual contouring of each slice, although there was

substantial variability across slices (more anterior slices required less time to completion). Approximately 11 to 13 hours were required to complete each patient's PFC measurements. Left and right PFC areas were contoured separately, and then summed. PFC volume was then corrected for TIV.

Intra-rater and inter-rater reliability were calculated by repeating PFC measurements across a randomly selected patient's MRI slices. Brightness and contrast ratios were held constant across slices. First, I completed PFC measurements across the first 11 slices for the patient, totaling 44 measurements altogether. To assess intra-rater reliability, these measurements were then erased, and the same patient's scans were measured again. One-tailed Pearson correlation analyses yielded adequate intra-rater reliability ($r[44] = .99$, $p < .001$). To assess inter-rater reliability, Dr. Craig Watson measured the same structures across the same slices for the patient, again holding brightness and contrast rations constant. Inter-rater reliability was also adequate ($r[44] = .97$, $p < .001$, one-tailed.)

Procedure

Ethics approval for secondary use of neuropsychological and MRI data from patients and control group individuals was received from the University of Windsor Research Ethics Board. Neuropsychological test data from patients with TLE were entered into a larger database for the Molecular Analysis of Human Epileptic Tissue project at WSU, a project that has IRB approval through WSU. As part of the neuropsychological assessment process, patients provided written informed consent for use of their data in research studies.

Patients were selected for participation by examining data from 65 consecutive patients referred for refractory TLE. To facilitate interpretability of results, only data from patients with unilateral hippocampal sclerosis were selected for the present study. Patients underwent a presurgical evaluation at the WSU Epilepsy Program, including

MRI scanning and comprehensive neuropsychological testing. Both MRI and neuropsychological assessment were completed to assess the potential clinical benefit of surgery. Patients were candidates for anterior temporal lobectomy surgery (ATLE) surgery to remove the area of epileptogenic focus.

Neuropsychological testing was conducted by clinical psychology graduate students from the University of Windsor or WSU who were completing practica with the Adult Neuropsychology Program in the Department of Neurology at the WSU School of Medicine. Testing lasted approximately six hours over the course of one day, and the order of tests administered was variable. No patients experienced seizures during the neuropsychological testing. MRI scans were performed within six months of neuropsychological testing.

Next, patient MRI volumetric data were entered into a Microsoft Excel database containing neuropsychological assessment data. This was then exported to SPSS 17.0 for Windows for statistical analyses. The alpha level was set at 0.05 for all analyses. Non-significant results are indicated in-text.

CHAPTER 3

Results

Preliminary Findings and Analyses

Sample size. At the outset of the study, it was anticipated that the size of the patient TLE sample would be at least 50 individuals. Due to issues with the MRI data, the sample size was significantly smaller (*n* = 38). Several of the MRI data files had become corrupted since their acquisition in the mid-1990s. When the SPGR images were originally obtained, they were first saved to a computer hard drive, then transferred to floppy disc, then transferred to CD ROM, then back to a hard drive, and so-on. Several times over the past fifteen years, as technology has developed, the MRI data have been transferred to different storage media. By the time of the current study, several patient scans were corrupted beyond repair.

Another reason the sample size was smaller than anticipated was that only data from individuals with unilateral hippocampal sclerosis was used. Individuals with evidence for bilateral sclerosis were excluded from the present study. Previous studies using this patient group included individuals with both bilateral and unilateral sclerosis, as well as a larger age range, yielding a considerably larger sample (e.g., Fuerst et al. 2003).

It was not possible to obtain more MRI data for this project. Around the turn of the century, the WSU School of Medicine switched the MRI protocol away from using SPGR images. Consequently, while there continue to be new TLE patients seen at WSU, the MRI data produced is not compatible with the volumetric process used in the current study.

Data analysis. As part of preliminary analyses, hippocampal volumes ipsilateral and contralateral to seizure onset were compared. Hippocampal volume ipsilateral to side of seizure onset was significantly less than hippocampal volume contralateral to

side of seizure-onset (*t*[37] = -15.5, *p* < .05; one-tailed). There was no difference between prefrontal volume either contralateral or ipsilateral to seizure onset (*t*[37] = 1.0*, ns;* one-tailed). Next, descriptive statistics for volumetric analyses (including both PFC and hippocampal volumes) and EF variables were calculated. The means and standard deviations of the MRI volumetric variables are presented in Table 3, while Table 4 contains means and standard deviations of the EF variables. In order to maximize power in the following analyses, left- and right-sided TLE patients were pooled into one sample, with hippocampal and prefrontal cortical volume coded as either ipsilateral or contralateral to side of seizure onset.

Core Analyses

Hypothesis 1. The first hypothesis was that individuals with medically refractory TLE would show impairment on several measures of EF. Inspection of the overall EF composite *z* score yielded support for the first hypothesis. Patients' individual composite *z* scores ranged from -2.45- to 0.73 (*M* = -0.76, *Mdn* = -0.65, *SD* = 0.80; 95% CI [-1.02, -0.5]), and a single-sample *t*-test indicated that the overall EF composite *z* score was significantly less than 0 (*t*[35]=-5.72, *p* < .01 [one-tailed]). The average of the overall composite EF *z* score corresponds with performance at the 22nd percentile.

Auxiliary analyses included inspection of the Trails B/A ratio. Part B of the Trail Making Test may be used alone to assess EF, (Bradford, 1992) as it is thought to reflect several aspects of EF (Sanchez-Cubillo et al., 2009; Ashendorf et al., 2008), especially cognitive shifting (Arbuthnott & Frank, 1999). When transformed into a ratio score, the visual perceptual and motor speed components of the Trails B task are reduced (Sanchez-Cubillo et al., 2009), helping to create a "relatively pure indicator" of EF (Sanchez-Cubillo et al., p. 438). Criteria outlined by Lamberty et al. (B/A ratio ≥ 3) were used to classify the B/A ratio as impaired. Using this cutoff value, eight of 34 patients

Table 3

MRI Volumetric Data for Left- and, Right-Sided TLE Patients and Neurologically Normal Control Group

	Left-Sided TLE (n=17)		Right-Sided (n=21)		Control Group (n=7)	
Volumetric Region of Interest	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Total intracranial volume	1,431,914	93,020	1,551,401	104,010	1,488,183	187,756
Left hippocampal volume	2,569	561	3769	332	3,756	424
Right hippocampal volume	3,590	393	3750	266	2,718	504
Left prefrontal volume[a]	59,107	8,124	89,590	16,085	65,467	13,337
Right prefrontal volume[a]	66,704	8,469	88,509	21,666	68,279	12,853
Left prefrontal cortical volume	41,012	5,756	39,459	8,550	45,023	8,952
Right prefrontal cortical volume	44,698	5,690	38,655	11,538	46,301	8,603

Note. All measurements presented in millimeters cubed.

[a] Represents *both* cortical and subcortical volume.

Table 4

Means and Standard Deviations of EF Measures for Left-Sided and Right-Sided TLE Patients

	Left-Sided TLE			Right-Sided TLE		
EF Measure	*n*	Mean	Standard Deviation	*n*	Mean	Standard Deviation
WCST[a] PE *z* Score	16	-0.06	1.40	18	-1.31	1.11
Digit Span[b] z score	16	-0.2	0.74	18	-0.18	1.04
Trails B[c] *z*	15	-0.06	1.13	19	-0.80	1.40
Trails B/A ratio z score	15	-0.09	0.97	19	-0.51	1.09
CVLT[d] Long-Delay Yes-No Discriminability *z* score	16	-1.25	1.23	18	-1.11	1.23
Semantic fluency[e] *z* score	15	-0.75	0.93	19	-1.18	1.35
Semantic fluency *z* switching score	15	-0.75	0.66	19	-1.06	1.07
Letter fluency[f] *z* Score	15	-0.63	0.93	18	-0.32	1.21
Letter fluency switching *z* score	15	-1.01	0.92	18	-1.16	1.29
Overall Composite z	16	-0.52	0.60	20	-0.84	0.99

Note. WCST = Wisconsin Card Sorting Test; PE = Perseverative errors; CVLT = California Verbal Learning Test.

[a] Wisconsin Card Sorting Test; Heaton et al., 1993. [b] Digit Span subtest from Wechsler Adult Intelligence Scale – Revised; Wechsler, 1987. [c]Trail Making Test Part B; Reitan & Wolfson, 1985. [d]California Verbal Learning Test; Delis, Kramer, Kaplan & Ober, 1987. [e]Semantic Fluency, Animal Naming; Tombaugh, Kozak, & Rees, 1999. [f]Controlled Oral Word Association test; Benton et al., 1994.

(24%) were classified as impaired. The Trails B/A ratio *z* score for these eight patients fell at or below -1.50, and ranged from -1.50 to -2.90.

Overall, the data supported the first hypothesis. When EF scores were collapsed into a single, overall composite *z* score, the overall composite score was significantly less than 0. This provides support for the first hypothesis because, if patients with TLE were performing in the average range on measures of EF, the overall composite z score would be statistically comparable to 0, the *z* distribution mean. When patient performance on the Trails B/A ratio was examined, 24% of the sample was classified as impaired.

Hypothesis 2. The second hypothesis posited that bilateral PFC volume would be positively correlated with performance on measures of cognitive shifting, updating, and inhibition. First, bilateral PFC volume was correlated with the overall EF composite *z* score calculated to assess hypothesis one (see above). Bilateral PFC volume was not significantly correlated with the overall EF composite *z* score $r(36) = -.24$, *ns,* (one-tailed).

In order to investigate the link between bilateral PFC volume and cognitive shifting, updating, and inhibiting (potentially hidden by creation of the overall EF composite *z* score), the associations between volume and individual test scores were computed. As noted above, each of these test scores has been associated in the literature with one or more of cognitive shifting, updating, and inhibition. The WCST PE *T* score was used to evaluate the potential link between bilateral PFC volume and inhibition. A one-tailed correlation analysis revealed no significant link between the WCST PE *T* score and bilateral PFC volume ($r[34] = -.13$, *ns*). The Trails B/A ratio *z* score was used to evaluate the relationship between bilateral PFC volume and cognitive shifting. A one-tailed correlation analysis revealed no significant link between the Trails B/A ratio *z* score and bilateral PFC volume ($r[34] = .13$, *ns*). To evaluate the association

between bilateral PFC volume and updating, the Digit Span Age Scaled Score from the WAIS-R was correlated with bilateral PFC volume. Again, a one-tailed correlation analysis showed no significant link between the Digit Span Age Scaled Score and bilateral PFC volume (r[34] = -.15, *ns*).

There was no evidence to support a relationship between bilateral PFC volume and performance on standardized EF measures among the patients in this sample. Additional analyses examining cognitive shifting, updating, and inhibiting separately (as assessed by the WCST PE T score, Trails B/A ratio z score, and Digit Span age-scaled score, respectively) showed no relationship between bilateral PFC volume and EF. Hypothesis two was not supported by the data.

Hypothesis 3. Recall that hypothesis three proposed that hippocampal volume ipsilateral to seizure onset would be positively correlated with bilateral PFC volume. A one-tailed correlation between hippocampal volume ipsilateral to seizure onset and bilateral PFC volume revealed no statistically significant relationship (r[38]=-.19, *ns*). As a supplementary analysis, hippocampal volume ipsilateral to seizure onset was correlated with PFC volume ipsilateral to seizure onset. Again, a one-tailed correlation revealed no significant association between the two areas (r[38] = -.10, *ns*). Hypothesis three was not supported by the data.

Hypothesis 4. ***Principal components analysis.*** A hierarchical multiple regression approach was planned to test hypothesis four, which postulated that hippocampal sclerosis and bilateral PFC volume would each add value to a linear model predicting performance on measures of EF in individuals with TLE. I intended to examine the effects of hippocampal volume on the side of seizure onset and bilateral PFC volume (after controlling for age and education) on measures of EF, using the protocol outlined by Quittner, Glueckauf, and Jackson (1990). This approach uses principal components analysis (PCA) to create a linear combination of dependent

variables. A benefit of the PCA approach is that it allows relative tolerance of multivariate abnormality (Briggs & MacCallum, 2003), a concern given the relatively small sample size in the present study. Using the recommendation of at least ten cases per variable (Nunnally, as cited by Field, 2005; Stevens, 2002), only three EF variables were entered into the analysis. The WCST PE *T* score, Trail Making Test Part B *T* score, and CVLT Long Delay Yes/No Recognition Discriminability *z* score were chosen for this analysis, given neuroimaging data showing PFC activation (as well as hippocampal activation, in the case of the CVLT) in these tasks (Haut et al., 1996; Johnson et al., 2001; Lie, Specht, Marshall, & Fink, 2006; Lombardi et al., 1999; Moll et al., 2002; Perry et al., 2009).

First, the assumptions of PCA were tested. The minimum amount of data for factor analysis was satisfied, with over 10 cases per variable. Data were screened for outliers using visual inspection of the data. Scatterplots were inspected to check for linearity of the data. The Kaiser-Meyer-Olkin measure of sampling adequacy was .59, above the minimum recommended value of .5. Bartlett's test of sphericity was significant (χ^2 (3) = 19.31 p < 0.01). Additionally, all communalities were well above .3 (see Table 7), further confirming that each item shared some common variance with other items. It was thus judged appropriate to continue with the PCA using the three variables.

Jolliffe's criterion (i.e., eigenvalues > .7) and Kaiser's criterion (i.e., eigenvalues > 1.0) as well as inspection of the Scree plot, were used to determine the number of factors to retain for rotation. Two components with an eigenvalue greater than 0.7 were extracted. The initial eigenvalues showed that the first factor explained 62% of the variance, the second factor 25% of the variance. This two-component solution was deemed adequate because it explained more than 87% of the overall variance.

According to the protocol outlined by Quittner et al. (1990) and to facilitate interpretation of components, varimax rotation was applied to the component scores

subsequent to extraction. Rotated component loadings and communalities are presented in Table 5. The first component was labeled *Switching* and the second component *Inhibiting*. Component scores were generated using the Anderson-Rubin method (Field, 2005).

Multiple regression analyses. It was predicted that hippocampal volume ipsilateral to seizure onset and bilateral PFC volume would each add predictive value to the EF factors component(s). In keeping with the nociferous cortex hypothesis, I hypothesized that bilateral PFC volume would mediate the relationship between hippocampal volume on the side of seizure onset and performance on measures of EF. In order to assess whether prefrontal volume mediated such a relationship, Holmbeck's (1997) approach to testing mediated effects was used. In this approach, three separate hierarchical regression analyses are advised: the first one to assess the degree to which the predictor A (hippocampal volume ipsilateral to seizure onset) predicts the mediator B (bilateral PFC volume). Assuming A is predictive of B, Holmbeck advises two more hierarchical regression analyses, the next examining the relationship between the predictor A and the outcome variable C (EF), requiring that predictors A and B are entered into the regression equation using simultaneous entry. In order for predictor B to be labelled a mediator variable, it must meet four conditions: 1) predictor B (bilateral PFC volume) must be significantly associated with predictor A (hippocampal volume ipsilateral to seizure onset); 2) predictor A must be significantly associated with the outcome variable C (EF); 3) predictor B must be significantly associated with the outcome variable C (EF); and 4) the impact of predictor A on the outcome variable is reduced after controlling for predictor B (Holmbeck, 1997).

Because the analyses were aimed at investigating the effects of hippocampal sclerosis, only hippocampal volume *ipsilateral* to epileptic focus was used in the regression analyses. For the regression analyses, hippocampal volume ipsilateral to

Table 5

Factor Loadings and Communalities Based on a Principle Components Analysis with Varimax Rotation for Three Measures of EF

EF Measure	Component One "Switching"	Component Two "Inhibiting"	Communality
CVLT[a] Long-Delay Yes-No Discriminabilty z score	.12	**.96**	.94
Trails[b] B T score	**.71**	**.53**	.78
WCST[c] Perseverative Error T score	**.94**	.05	.90

Note. Factor loadings >0.5 are in boldface. WCST = Wisconsin Card Sorting Test; CVLT = California Verbal Learning Test.

[a] California Verbal Learning Test; Delis, Kramer, Kaplan & Ober, 1987. [b]Trail Making Test Part B; Reitan & Wolfson, 1985. [c]Wisconsin Card Sorting Test; Heaton et al., 1993.

seizure onset and bilateral PFC volume were used as predictors for the two EF components described above. For each regression analysis, data were first examined to ensure the assumptions of the technique were upheld. For all analyses, inspection of the Mahalanobis distance ratings showed no extreme multivariate outliers. Homoscedasticity was examined via several scatterplots and review of studentized residuals. Both consistently indicated reasonable consistency of spread through the distributions. Correlations among predictor variables were small to moderate, ranging from 0.01 (hippocampal volume ipsilateral to seizure onset and total years of education) to -0.55 (bilateral PFC volume and age). This indicated that multicollinearity was unlikely to be a problem.

The first regression analysis tested whether hippocampal volume ipsilateral to epileptic focus was a significant predictor of bilateral PFC volume, after controlling for age and education. On the first step, age and education were entered simultaneously into the model. They were significantly associated with bilateral PFC volume, producing an adjusted R^2 of .28 ($F(2, 33) = 8.04$ $p < .01$). On the second step, hippocampal volume ipsilateral to epileptic focus was entered into the model, resulting in a non-significant ΔR^2 (see Table 6). While the results of this analysis did not show that hippocampal volume ipsilateral to seizure onset was predictive of bilateral PFC volume (a necessary condition for the hippocampal hypothesis and for bilateral PFC volume to mediate the relationship between hippocampal volume and EF), Holmbeck's approach to testing mediating effects was continued, for descriptive purposes only.

As auxiliary analyses, hierarchical multiple regression analyses were conducted to predict component scores for *Switching* and *Inhibiting*. For these analyses, only education was entered as the first step in the model, as age-adjusted scores were used to create the component score(s). First, two regression analyses predicting *Switching* were conducted. In the first analysis, education was entered as the first step of the

Table 6

Results of Forced-Entry Regression Analysis Examining Effects of Age, Education, and Hippocampal Volume and Bilateral Prefrontal Volume

Predictor	*R*	R^2	ΔR^2	*F*	*df*	B^*_i	*n*
Step 1	.57	.32	.32	8.04	2,33		38
Age						-.59*	
Education						.14	
Step 2	.57	.33	.00	5.24	3,32		38
Hippocampal volume ipsilateral to seizure onset						-0.5	

*p<0.001.

model. Hippocampal volume ipsilateral to seizure onset was entered as the second step. Neither education nor hippocampal volume ipsilateral to seizure onset were predictive of the *Switching* component score (see Table 7). As per Holmbeck's protocol for testing mediation effects, in the second regression analysis predicting *Switching,* education was again entered as the first step of the model, with bilateral PFC and hippocampal volume ipsilateral to seizure onset entered as the second step. Neither step of the model was significant (see Table 8).

Tables 9 and 10 show parallel hierarchical regression analyses for *Inhibiting* component scores. While hippocampal volume ipsilateral to seizure onset did not add any predictive value to either regression model, bilateral prefrontal volume added significant predictive value in the second step of the second regression analysis (see Table 10).

Even though bilateral PFC volume contributed significantly to a regression model predicting the second EF component, *Inhibiting*, there was, overall, no evidence to support either the nociferous cortex hypothesis or the hippocampal hypothesis. Hypothesis four posited that hippocampal volume ipsilateral to seizure onset and bilateral PFC volume would each add statistical value to a linear model predicting performance on measures of EF. Instead, there was no significant relationship between hippocampal volume ipsilateral to seizure onset and EF, providing no support for the hippocampal hypothesis. The nociferous cortex hypothesis required that bilateral PFC volume mediate the relationship between hippocampal volume ipsilateral to seizure onset and EF. This was not supported by the data. First, there was no relationship between hippocampal volume ipsilateral to seizure onset and bilateral PFC volumes, or between hippocampal volume and EF (as noted above), and the relationship between bilateral PFC volume and EF was weak at best. Indeed, regression analyses showed

Table 7

Results of Forced-Entry Regression Analysis Examining Effects of Education and Hippocampal Volume on Principle Component Switching

Predictor	*R*	R^2	ΔR^2	*F*	*df*	B^*_i	*n*
Step 1	.09	.00	.00	0.26	1,31		33
Education						.09*	
Step 2	.12	.01	.00	.25	2,30		33
Hippocampal volume ipsilateral to seizure onset						.09*	

*$p > 0.05$.

Table 8

Results of Forced-Entry Regression Analysis Examining Effects of Education, Hippocampal Volume, and Bilateral PFC Volume on Principle Component Switching

Predictor	*R*	R^2	ΔR^2	*F*	*df*	B^*_i	*n*
Step 1	.09	.00	.02	0.26	1,31		33
Education						.09*	
Step 2	.28	.07	.06	0.80	3,29		33
Hippocampal volume ipsilateral to seizure onset						.04*	
Bilateral PFC volume						-.25*	

*$p > 0.05$.

Table 9

Results of Forced-Entry Regression Analysis Examining Effects of Education and Hippocampal Volume on Principle Component Inhibiting

Predictor	*R*	R^2	ΔR^2	*F*	*df*	B^*_i	*n*
Step 1	.25	.06	.06	2.12	1,31		31
Education						.25*	
Step 2	.27	.07	.01	1.18	2,30		31
Hippocampal volume ipsilateral to seizure onset						.09*	

*$p > 0.05$.

Table 10

Results of Forced-Entry Regression Analysis Examining Effects of Education, Hippocampal Volume, and Bilateral PFC Volume on Principal Component Inhibiting

Predictor	*R*	R^2	ΔR^2	*F*	*df*	B^*_i	*n*
Step 1	.25	.06	.06	2.12	1,31		31
Education						.25	
Step 2	.43	.19	.12	2.28	3,29		31
Hippocampal volume ipsilateral to seizure onset						.16	
Bilateral PFC volume						.35*	

*p<0.05.

that bilateral PFC volume contributed significantly to only one regression equation, predicting the second component score.

Hypothesis 5. ***Principal components analysis***. Hypothesis five held that hippocampal volume ipsilateral to epileptic focus and bilateral PFC volume would be more strongly predictive of performance on standardized tests of verbal memory, EF, and psychomotor speed than of performance on tests of visual perceptual abilities, confrontation naming, and global intellectual functioning. In order to test across multiple cognitive domains, a linear combination of scores on EF, memory, and psychomotor speed was created (outcome A, see Table 11). A linear combination of scores on global intelligence, confrontation naming, and visual perceptual abilities was also created (outcome B, see Table 12).

Given the size of the sample, only three test scores were used to create each component. To assess verbal memory, the total number of words recalled across the five learning trials of the CVLT was used. Total recall over the five learning trials was transformed into a standardized *z* score using age-scaled normative data. The CVLT total recall *z* score was chosen to assess verbal memory, given that this score is known to be sensitive to a variety of disorders, including TLE (Elwood, 1995). EF was assessed using the WCST PE *T* score, which previous research has demonstrated may be impaired in individuals with TLE (Corcoran & Upton, 1993; Giovagnoli, 2001). In order to limit the number of variables used in the PCA, psychomotor speed was assessed using the Trail Making Test Part A *T* score rather than using bilateral motor dexterity *T* scores. The JOLO percentile score (corrected for age and gender) was used as the measure of visual perceptual abilities for hypothesis five. The JOLO has been described as one of the ”purest” measures of visual perceptual abilities (Mitrushina, Boone, Razani, & D’Elia, 2005, p. 284), given that it requires minimal verbal and/or motor skills. Confrontation naming was tested using the Visual Naming subtest of the Multilingual

Table 11

Tests, Scores, Factor Loadings, and Communalities of Outcome Variable A

Domain	Test	Score	Component Loading	Communalities
Memory	CVLT[a]	Total Learning (Trials 1-5) *z* score	**.70**	.50
Executive Function	WCST[b]	Perseverative Error *T* score	**.76**	.58
Psychomotor Speed	Trail Making Test[c] Part A	*T* score	**.76**	.58

Note. Factor loadings >0.5 are in boldface. CVLT = California Verbal Learning Test; WCST = Wisconsin Card Sorting Test.

[a] California Verbal Learning Test; Delis, Kramer, Kaplan & Ober, 1987. [b]Wisconsin Card Sorting Test; Heaton et al., 1993. [c]Trail Making Test Part B; Reitan & Wolfson,

Table 12

Tests, Scores, Factor Loadings, and Communalities of Outcome Variable B

Domain	Test	Score	Component Loading	Communalities
Visuoperceptual Abilities	JOLO [a]	Percentile	.41	.64
Confrontation Naming	MAE - Visual Naming Test[b]	Percentile	.40	.76
Global Intelligence	Wechsler Adult Intelligence Scales – Revised[c]	Full Scale IQ Standard Score	.36	.79

Note. JOLO = Judgment of Line Orientation Test; MAE = Multilingual Aphasia Exam.

[a] Judgment of Line Orientation Test; Benton et al., 1994. [b]Visual Naming Test; Benton, Sivan, et al., 1994. [c] Full Scale Intelligence Standard Score from Wechsler Adult Intelligence Scale – Revised; Wechsler, 1987.

Aphasia Exam, as this was the only confrontation naming measure used in the neuropsychological assessment battery. Finally, global intellectual function was assessed using the Full Scale IQ from the WAIS-R.

The assumptions of PCA were tested for both analyses. For both outcomes A and B, there were at least ten cases per variable. No outliers were evident upon visual inspection of the data, and scatterplots were inspected to check for linearity of the data. For outcome A, all three variables correlated at least .31 with at least one other variable suggesting adequate factorability, and the Kaiser-Meyer-Olkin measure of sampling adequacy was .63, above the recommended value. Bartlett's test of sphericity was significant (χ^2 (3) = 8.85). Communalities were all above .50, confirming that each variable shared some common variance with other variables.

For outcome B, all three variables correlated at least .45 with at least one other variable, suggesting adequate factorability, and the Kaiser-Meyer-Olkin measure of sampling adequacy was .65, above the recommended value. Bartlett's test of sphericity was significant (χ^2 (3) = 21.25). Communalities were again all above .50, confirming that each item shared some common variance with other items.

For both outcome variables, Jolliffe's criterion and Kaiser's criterion were examined, as were Scree plots, to determine the number of factors to extract. One component with an eigenvalue greater than 1.0 was extracted for outcome A; one component was also extracted for outcome B. The first component (outcome A) explained 55% of the variance in the data, while the second (outcome B) explained 73% of the variance in the data. As only one component was extracted in each PCA, rotation was not applied. Component loadings are presented in Table 11 (for outcome A) and Table 12 (for outcome B). Component scores were again generated using the Anderson-Rubin method (Field, 2005).

Multiple regression analyses. To test hypothesis five, two regression analyses were run, and the predictive contribution of hippocampal volume ipsilateral to seizure onset and bilateral PFC atrophy were compared across the two models. For both analyses, the assumptions of the regression technique were met. A hierarchical approach was used to ensure that the two analyses would be sufficiently similar to meaningfully interpret any differences in the results. Accordingly, education was entered as the first step in the regression, followed by hippocampal volume ipsilateral to seizure onset, as well as bilateral PFC volume. Model characteristics for outcome A are presented in Table 13, and model characteristics for outcome B are presented in Table 14.

Hypothesis five posited that the model predicting EF, memory, and psychomotor speed would show a better fit than the model predicting visuoperceptual abilities, confrontation naming, and global intelligence. Given that the neither regression model showed significant predictive value of hippocampal volume ipsilateral to seizure onset and bilateral PFC volume, hypothesis five was not supported by the data.

Table 13

Results of Forced-Entry Regression Analysis Examining Effects of Education, Hippocampal Volume, and Bilateral PFC Volume on Outcome A

Predictor	*R*	R^2	ΔR^2	*F*	*df*	B^*_i	*n*
Step 1	.22	.05	.05	1.14	1,21		23
Education						.23*	
Step 2	.51	.26	.21	2.29	3,19		23
Hippocampal volume ipsilateral						.36*	
Bilateral PFC volume						-.22*	

*$p > 0.05$.

Table 14

Results of Forced-Entry Regression Analysis Examining Effects of Education, Hippocampal Volume, and Bilateral PFC Volume on Outcome B

Predictor	*R*	R^2	ΔR^2	*F*	*df*	B^*_i	*n*
Step 1	.34	.11	.08	4.10	1,31		33
Education						.34*	
Step 2	.42	.17	.09	2.10	3,29		33
Hippocampal volume ipsilateral						.19*	
Bilateral PFC volume						-.11*	

*$p > 0.05$.

Chapter Four

Discussion

The purpose of the current study was to investigate EF deficits in individuals with TLE, as well as the link between PFC and hippocampal volume and the extent to which both relate to EF deficits in these individuals. Neurocognitive deficits, including EF impairments, have been repeatedly demonstrated in individuals with refractory TLE (Dabbs et al., 2009; Dodrill, 2008; Helmstaedter, 2005; Jokeit, & Ebner, 2002; Oddo et al., 2006; Martin et al., 2005; Schachter et al., 2006; Zhang et al., 2009). Medically refractory TLE is hallmarked by hippocampal sclerosis, and neuroimaging has demonstrated that increased hippocampal atrophy is associated with progressive, concomitant decrease in volume of distal areas, including the PFC (Bernasconi et al., 2010; Bernhardt et al., 2008; Bernhardt et al., 2009; Coan et al., 2009; Keller et al., 2009). As the relationship between the PFC and EF has been well documented, I predicted that reduced bilateral PFC volume would be associated with hippocampal sclerosis, and that both would in turn be associated with EF deficits. Structural neuroimaging was used to determine whether hippocampal volume on the side of seizure onset and/or bilateral PFC volume were associated with EF deficits. The former association would provide support for the hippocampal hypothesis; the latter, for the nociferous cortex hypothesis.

Statement of Major Findings

Presence of EF impairments. These results demonstrate that individuals with refractory TLE show impaired EF. I hypothesized that individuals with refractory TLE would show impairment on several standardized measures of EF. When EF scores were combined into a composite *z* score, the mean composite score for the sample was significantly below the mean expected for a normal group. Additionally, approximately

one quarter of the sample demonstrated impairment on a well-recognized measure of EF (the Trails B/A ratio).

Bilateral PFC volume and EF. While there was evidence for EF impairment in this sample, there was no evidence for a relationship between bilateral PFC volume and EF, as had been hypothesized. Bilateral PFC volume was not correlated with the overall EF composite, nor with specific test scores reflecting cognitive shifting, updating, and inhibiting. There was no evidence for a link between structural integrity of the PFC and the EF measures used in the current study.

Hippocampal sclerosis and bilateral PFC volume. Further, bilateral PFC volume was not significantly associated with hippocampal volume ipsilateral to seizure onset (hippocampal sclerosis). There was no evidence for a relationship between hippocampal and bilateral PFC volume in the current study.

Hippocampal sclerosis, bilateral PFC volume, and EF. The fourth hypothesis posited hippocampal sclerosis ipsilateral to seizure onset and bilateral PFC volume would each add value to a linear model predicting performance on measures of EF in individuals with TLE, even after controlling for age and education. According to the protocol outlined by Quittner and her colleagues (1990), PCA was used to create two EF components *Switching* and *Inhibiting*, and factor scores were generated for each patient. Multiple regression analysis showed that hippocampal sclerosis was not significantly predictive of bilateral PFC volume, a necessary predicate for PFC to mediate the relationship between hippocampal sclerosis and EF. Therefore, the data did not support the nociferous cortex hypothesis.

Furthermore, there was no evidence to support the hippocampal hypothesis. To investigate the hippocampal hypothesis, hippocampal volume ipsilateral to seizure onset was entered as a predictor into two separate multiple regression analyses predicting the EF components *Switching* and *Inhibiting*. Inspection of results showed that hippocampal

volume was not predictive of either. Overall, neither the hippocampal hypothesis nor the nociferous cortex hypothesis was supported by the data.

A third set of regression analyses were then run, entering both hippocampal volume ipsilateral to seizure onset and bilateral PFC volume simultaneously into regression equations predicting the *Switching* and *Inhibiting* component scores. Again, there was no evidence that hippocampal volume was predictive of EF. However, bilateral PFC volume contributed significantly to the regression model predicting the *Inhibiting* component. Overall, the data provided little evidence for either the nociferous or hippocampal hypotheses.

TLE and other cognitive domains. Finally, based on the work of Hermann, Seidenberg, and their colleagues (e.g., Dabbs et al., 2009; Hermann & Seidenberg, 1995; Herman et al., 2003; Hermann et al., 1991; Hermann et al, 2007; Hermann et al., 1988; Oyegbile et al., 2004; Seidenberg et al., 1998), I predicted that hippocampal sclerosis and bilateral PFC volume would be more predictive of EF, psychomotor speed, and memory, than of global intellectual functioning, visual spatial abilities, and naming. Using PCA, two factor scores were generated: the first factor represented patient performance on EF, psychomotor speed, and memory, while the second represented patient performance on general intellectual functioning, visual spatial abilities, and confrontation naming. Hierarchical regression analyses showed that neither hippocampal sclerosis nor bilateral PFC volume were predictive of either factor.

EF Deficits in TLE

Overall, individuals with medically refractory TLE and unilateral hippocampal sclerosis demonstrated impairment on a composite based on several standardized measures of EF. This is consistent with previous research, which has demonstrated EF deficits in similar groups (e.g., Dabbs et al., 2009; Hermann & Seidenberg, 1995; Hermann et al., 2007; Hermann et al., 1988; Keller et al., 2009; Martin et al., 2000;

Martin et al., 2005; Seidenberg et al., 1998; Shulman, 2000; Silvia et al., 2003; Zhang et al., 2009). EF deficits have been observed using standardized neurocognitive tests as well as measures of decision making ability (Labudda et al., 2009) and social cognition (Schacher et al., 2006). The current results provide convergent evidence for EF impairment in individuals with refractory TLE, and these data serve to highlight the importance of testing for EF impairments in these patients. While memory impairment in patients with refractory TLE is widely acknowledged (see Dodrill, 2008; Helmstaedter, 2005; Oddo et al., 2006), EF impairments may not be as well documented and so not as well recognized. This is of significant clinical relevance for neuropsychologists who are assessing patients with refractory TLE, as it reinforces the importance of including EF measures in the pre-surgical neuropsychological test battery.

Functional integrity of the PFC. The etiology of the below normal scores on EF measures observed in the current sample remains unclear. There was no evidence that structural integrity of bilateral PFC and sclerotic hippocampi were associated with performance on the EF measures used in the current study. A possible explanation for these non-significant findings may lie in a functional, rather than structural effect of hippocampal sclerosis on bilateral PFC. Hippocampal sclerosis may create functional rather than structural changes in distal areas, for example, by inhibiting function in these areas. This mechanism has been well documented (e.g., Squire, 1992; Stark, 2007; Zola-Morgan et al., 1986; Zola-Morgan et al.,1989). Dysfunction in regions of the PFC in both hemispheres—rather than structural changes—may produce negative changes in EF.

When we consider other progressive neuropathologies, reduced cortical volume is almost always preceded by physiological disruption of cortical function. This is the case in both Alzheimer's disease and chronic traumatic encephalopathy, where neurocognitive functioning often declines before volume reduction is apparent on

structural imaging scans (Mendez & Cummings, 2003). Physiological disruption of an area is often accompanied by gliosis and eventual atrophy of the affected tissue. In the case of refractory TLE, early hippocampal sclerosis may be associated with disruption of white matter tracts or it may change the neurophysiology but not the structural integrity of distal cortex (including the PFC). As such, it may be that hippocampal atrophy is apparent before any distal volume reductions are visible, despite the fact that distal tissue may be *already functionally disrupt*ed. The present study did not allow for investigation of the functional integrity of the PFC, or the fronto-temporal networks, and this is an area deserving further investigation (see below).

TLE, depressed mood, and EF. Another possible etiology for EF deficits in this sample is the negative mood symptoms reported by patients. Almost 50% of all patients in this sample reported clinically significant symptoms of depression on the MMPI-2 or BDI. Fourteen patients (37%) had already been formally diagnosed with major depression at the time of the neuropsychological assessment. Depression is often comorbid with refractory TLE (Helmstaedter, 2004; Reuber, Anderson, Elger, & Helmstaedter, 2004; Schmitz, 2005) and Paradiso, Hermann, Blumer, Davies, and Robinson (2001) have demonstrated that depression is negatively correlated with performance on EF measures in this patient population.

It remains unclear whether depression is the product, the cause, or a common endpoint of EF disruption. The neuropsychological literature contains many examples of the relationship between negative mood and executive dysfunction (e.g., Agganis et al., 2010; Bour, Rasquin, Limbug, & Verhey, 2010; Klepac, Hajnsek, & Trkulja, 2010) in several different patient groups. Longitudinal studies also suggest that otherwise neurologically normal individuals with depressive symptoms are at higher risk for EF deficits, although the mechanism is not certain (Cui, Lyness, Tu, King, & Caine, 2007) and includes “mood-cognitive interactions” (Fossati, Ergis, Allilaire, 2002, p. 97). Overall,

the potentially deleterious impact of negative mood on the EF impairments seen in this sample cannot be discounted.

Hippocampal Sclerosis and Distal Cortical Atrophy

Several studies have demonstrated progressive cortical thinning in several areas of tissue, including the PFC, as hippocampal sclerosis progresses (e.g., Keller & Roberts, 2008). Current results did not show any evidence for a link between bilateral PFC volume and hippocampal sclerosis. Even though the present study did not track PFC volume longitudinally, it is notable that hippocampal and bilateral PFC volume were not significantly correlated. Extrapolation from previous studies would suggest that reduced hippocampal volume (sclerosis) is associated with reduced PFC volume, as well as reduced volume in other areas of distal cortex. For example, Bernhardt et al. (2009) found that bilateral PFC decreased by 0.05mm^3 each year as hippocampal sclerosis progressed.

The discrepancy between current results and those mentioned above (Bernhardt et al., 2008; Bernhardt et al., 2009; Coan et al., 2009; Dabbs et al., 2009; and Lin et al., 2007) may be related to differences in MRI software protocol, study design, and perhaps most notably, in sample selection.

Automated versus manual volumetric software. The studies discussed above used automated volumetric software (e.g., VBM) in their analyses, while the present study used manual contouring. Although automated volumetric programs tend to be more efficient in mapping volumetric data, some have critiqued their validity and reliability. As many free automated volumetric software programs are available in the public domain (e.g. scanSTAT [Cohen & Scheding, 1998]; Freesurfer [http://surfer.nmr.mgh.harvard.edu]), the automated approach to MRI volumetric analysis is very widely used. In most automated protocols, MRI images are transformed and then transposed onto Talairach space. Grey and White matter are detected and segmented

using a computer algorithm, non-brain tissue is removed from the image, and ROI measurements are made entirely by the computer (e.g., Fischl et al., 2002; Fischl et al., 2004a). This approach has been described as "less time-consuming" than manual contouring (Hsu et al., 2007, p. 5; Ambarki, Wahlin, Birgander, Eklund, & Malm, 2011; Chow et al., 2007). Automated contouring appears to be the most popular approach to MRI volumetric analysis at present.

Although the automated approach to MRI volumetric analysis has produced a plethora of peer-reviewed studies, it is not without its critics. Some have claimed that the automated approach to MRI volumetrics favours efficiency at the expense of accuracy. While the automated approach requires less time than a manual contouring procedure, it has been critiqued for its tendency to smooth or flatten images (Tosun et al. 2004): as a result, gyri and sulci may be obscured. This has been described as the "problem of buried cortex" (Magnotta et al., 1999, p. 151), and was particularly problematic for the earlier automated software programs (Lerch, 2005). Some neurologists and neuroradiologists have gone so far as to argue that the automated approach to MRI produces data that are less accurate, valid, and reliable than that produced by the manual contouring approach (C.R. Watson, personal communication, December 4, 2010).

A study comparing manual and automated measurements of hippocampi found that the automated measurements were less reliable than manual measurements (Hsu et al., 2007). Hsu and colleagues (2007) concluded that automated MRI measurements may contain more image noise and variable automated warping, making measurements less reliable. The authors describe manual contouring as the "gold standard" of volumetric analysis (Hus et al., 2007, p. 5). Other studies have found similarly different measurements when comparing automated and manual contouring of the same ROI

(e.g., Ambarki et al., 2011; Kennedy et al., 2009; Pardoe, Pell, Abbott, & Jackson, 2009; Riffkin et al., 2005).

While the automated approach is valuable for its speed and efficiency, manual contouring of brain tissue "remains the reference method" of choice (Ambarki et al., p. 408). The manual approach to completing volumetric analysis, while time consuming, may be more accurate than automated protocols, especially with regard to cortical surfaces.

Differences in study design. Another potential explanation for the inability of the current study to replicate previous research showing distal cortical thinning in patients with hippocampal sclerosis relates to the design of the study itself. Previous studies have shown distal cortical thinning (including PFC thinning) in patients with refractory TLE. Importantly, any conclusion about thinning requires comparison between one measurement and another. In some studies discussed above, patient ROI measurements were compared against a normal control group (between-subject design), while other studies used longitudinal data (within-subject design) to compare different data points. Unfortunately, data available for the current study did not allow for either between or within subject design of patient ROI measurements. The control group was judged too small (n = 7) to use for a between-subject comparison, and longitudinal data was not available for the TLE patients in the present study. As a result, current data allowed for only a point-point correlation between hippocampal and PFC volume, rather than any changes in PFC volume over time, or any measures of PFC atrophy (compared against a normal control group).

Pure hippocampal sclerosis. Perhaps the most central reason that the current study was not able to replicate data showing a relationship between bilateral PFC volume and hippocampal sclerosis (e.g., Keller et al., 2009) may be the criteria used to select participants. When patients were originally selected for inclusion in studies

examining hippocampal volume (e.g., Watson et al., 1997), only individuals with discrete neuropathology in the parahippocampal cortex were selected. Stated differently, only individuals with unilateral gliosis and atrophy of the CA1 sector and subiculum of the hippocampal formation, and *no other neuropathologies*, were included in the analyses. Accordingly, any individuals with obvious atrophy in distal cortical areas (such as the frontal lobe) were excluded.

These selection criteria may help to explain the difference between current results and those of previous studies showing a link between hippocampal sclerosis and distal cortical volume (e.g., Bernasconi et al, 2010; Bernasconi et al., 2005; Bernhardt et al., 2008; Bernhardt et al., 2009; Dabbs et al., 2009; Keller et al., 2009; Hermann et al., 2003, 2007; Oyegbile et al., 2004). It is likely that these studies included TLE patients with more heterogenous neuropathology, and did not limit their samples to only those patients with discrete unilateral hippocampal sclerosis. For example, Keller et al. (2009), who found significant correlations among hippocampal volume and PFC in individuals with refractory TLE, used data from "forty-three non-consecutive patients… retrospectively selected from a large clinical database of patients" (p. 187). More precise selection criteria are not specified. It is possible that the patients in the Keller et al. (2009) sample were selected for analyses specifically because they demonstrated reduced prefrontal volume and/or EF deficits, and, if that is the case, the discrepancy between current results and those of Keller et al. is not surprising.

Clinical Implications

With respect to more direct clinical implications, the level of EF impairment demonstrated by individuals in this sample reminds clinicians that patients with refractory TLE may present with deficits or weaknesses in several different cognitive domains. Current results will continue to educate neuropsychologists (and other treating clinicians)

about neurocognitive status in patients with similar demographic characteristics to those described here.

These results also have implications for clinical care and case management. Some epileptologists argue that individuals are appropriate candidates for epilepsy surgery as long as they show only mild cognitive impairment (Polkey & Binnie, 1993). Those who are impaired across several cognitive domains are not thought to be good candidates for resective epilepsy surgery such as ATLE (Danielsson, 2008; Polkey & Binnie, 1993). That the TLE patients in this sample (all of whom were candidates for ATLE) as a group showed evidence for EF impairment suggests that EF deficits in these individuals may be more common than otherwise thought, and evaluation of candidates for epilepsy surgery should take this into account.

Additionally, while a few published studies have examined the effects of memory rehabilitation (Helmstaedter et al., 2008; Hendricks, 2001; Ponds & Hendricks 2006) in individuals with TLE, none have focused on rehabilitation of executive dysfunction in this patient group. Based both on current results as well as previous studies demonstrating EF impairment in patients with TLE, research is needed about cognitive rehabilitation of executive dysfunction in these patients. Cognitive rehabilitation of executive dysfunction may be especially important, given the evidence that EF impairment remains even after hippocampal resection (Seidenberg et al. 1998). It may be that patients with TLE may benefit from cognitive remediation and rehabilitation of EF deficits both before and after ATLE surgery.

Finally, the current study serves as yet another caution against using structural neuroimaging to make inferences about neurocognitive functioning. Despite the time and expense associated with comprehensive neuropsychological assessment (e.g., Schomer, 2000), the information such assessments produce remains essential for high quality care for patients with refractory TLE. Information about patient neurocognitive

and emotional status cannot reliably be inferred using either structural or functional neuroimaging procedures.

Comments and Limitations

In this study, there are some important limitations to the interpretation and generalizability of the results related to sample size, sample characteristics, and external validity. Because of the MRI volumetric protocol used in the current study, it was not possible to obtain more patient data for analysis. While the sample size is similar to those of other published studies on patients with TLE, the small *n* limited the nature, number, and statistical power of inferential statistics used in the analyses. For patients with refractory TLE, reductions in PFC and other neocortical volume may be quite subtle; as such, a much larger sample size may be needed to have sufficient data to uncover it.

As noted above, the current sample was limited to those patients with relatively pure hippocampal sclerosis. Such discrete neuropathology may not generalize well to the full range of individuals with refractory TLE, who may also report comorbid neurological disorders such as head injuries (Davis et al., 2005). As such, the homogeneity of the current sample may be considered a limitation of the study.

Finally, although the current results present evidence for impairment on standardized neuropsychological tests, it is difficult to speak to patients' EF in everyday life. Impairments on the standardized neuropsychological measures used in the current study may suggest a relatively greater level of functioning than may be regularly observed in the real world. Standardized neurocognitive assessments do not assess how a patient would perform during totally novel, ambiguous, complex, or self-motivated activities; nor do they look at unstructured, naturalistic instances of memory, attention, and judgement (Chaytor & Schmitter-Edgecombe, 2003). As a result, the standardized neuropsychological tests used in this study may overestimate EF as it would be expressed in daily life. EF deficits, even when considered to be *mild*, can have significant

and wide-reaching functional impact (Horton & Reynolds, 2007). Accordingly, the level of EF impairment observed in the current sample might underestimate the EF deficits the patients experience in their daily lives.

Future Directions

It is important to reiterate that the current investigation was essentially the first of its kind to examine manually-contoured bilateral PFC volumes in patients with refractory TLE. It is also the first to examine the joint effects of hippocampal sclerosis and bilateral PFC volume on EF performance in these individuals. Current findings should be replicated with a different sample in order to examine generalizability to the broader TLE population. Future research should also examine cortical volume in this patient group using both automated and manual contouring procedures (similar to the comparison run by Hsu et al., 2007).

It is also important to note that the current study is unable to identify the physiological or functional integrity of the ROIs examined above. Functional neuroimaging research (e.g., PET) should examine PFC hypometabolism in this patient group. Additionally, DTI protocols would allow for investigation of the integrity of fronto-temporal and specifically the fronto-limbic tracts. Functional imaging procedures would help address the normality of functioning of distal cortical tissue (and the PFC in particular) in patients with refractory TLE.

Further, it would be valuable to follow EF longitudinally in patients with TLE. It may be that EF deteriorates over time as hippocampal sclerosis progresses. As some patients refuse ATLE surgery (Polkey & Binnie, 1993), it would be also be possible to follow EF across time, both in patients who have had their epileptic focus removed, and in those who have not. This type of data would allow for continued investigation of the nociferous cortex and hippocampal hypotheses and may help speak to the etiology of EF deficits in individuals with refractory TLE.

Finally, while the current research demonstrated EF impairment on standardized neuropsychological measures of EF, it would also be appropriate to examine behavioural analogues of EF measures in this patient group. Use of clinical questionnaires to report symptoms of executive dysfunction would be appropriate (e.g., Behaviour Rating Inventory of Executive Function [Gioia, Isquith, Guy, & Kenworthy, 2000]; Frontal Systems Behavior Scale [Grace & Malloy, 2001]), as would standardized behavioural assessments (e.g., the Kingston Standardized Behavioural Assessment, [Hopkins, Kilik, Day, Bradford, & Rows, 2006]; or the Neurobehavioural Rating Scale – Revised [NRS-R]; Levin et al. as cited by McCauley et al., 2001).

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