An Investigation of Extra-Temporal Deficits in Temporal Lobe Epilepsy

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DEDICATIONS

To my incredibly patient family (especially John, Michael and Matthew) and friends who have supported me through a very long and arduous process. Many times I wavered, but they would not allow me to abandon my dreams and ambitions. Most of all, to the two people who demonstrated total confidence in my ability and provided me with unconditional support and enthusiasm to the very end, Ed and Gloria Weisse, my parents. Thank you.
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ABSTRACT

An Investigation of Extratemporal Deficits in Temporal Lobe Epilepsy
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Temporal lobe epilepsy (TLE) is a chronic disorder characterized by recurrent seizures arising from temporal lobe structures. Circumscribed unilateral focal seizures of temporal lobe origin have been associated with cognitive deficits outside of the seizure focus site in the medial temporal lobe (Corcoran & Upton, 1993; Hermann & Seidenberg, 1995; Trennery & Jack, 1994). The purpose of this study was to test the hypothesis that extratemporal deficits exist among patients with unilateral temporal lobe epilepsy. Presurgical test data from eighty patients with simple or complex partial seizures were examined for the purposes of exploring extratemporal impairment of function. Postsurgical test data were also examined for evidence of recovery of cognitive function. It was predicted that extratemporal deficits would be more prominent among patients with left temporal lobe epilepsy than among patients with right temporal lobe epilepsy. These deficits represent impairment of ipsilateral frontal and contralateral temporal lobe regions. It was also hypothesized that post-surgical recovery of function would occur in patients with good seizure control as compared to patients with poor seizure control. Extratemporal deficits were established in frontal and contralateral regions. These deficits were not more apparent in the left temporal lobe epilepsy group than in the right temporal lobe epilepsy group. Post-surgical scores did not reflect recovery of function in patients with good seizure control as compared to patients with poor seizure control on measures of extratemporal functions.
1. INTRODUCTION

Temporal lobe epilepsy is a seizure disorder affecting over one million Americans. Its social, psychological, physiological, and cognitive aspects affect a large number of people over a major portion of their lives. Temporal lobe epilepsy is associated with cognitive deficits that result from lesions of the temporal lobe and related limbic regions. Recent investigations using functional imaging techniques have detected dysfunction in patients with temporal lobe epilepsy that extends to remote areas outside of the epileptogenic zone. A thorough examination of temporal lobe epilepsy and its accompanying neuropsychological and neuroanatomical correlates may help to elucidate the manner in which these deficits occur. The following study examined the type and pattern of cognitive deficits in temporal lobe epilepsy that are representative of regions outside of the epileptogenic temporal region. The study also examined recovery of function following surgery that removed the epileptogenic focus.

1.1 Seizure Disorders and Syndromes

1.1.1 Seizure disorders.

Epilepsy is a chronic neurological disorder involving recurrent and unpredictable seizures (Fisher et al., 2005). A seizure is a synchronized paroxysmal event caused by an excessive electrical discharge of central nervous system neurons (Lowenstein, 2004). The normal function of neurons is to produce electrochemical signals that act on other neurons, glands and muscles to produce functions such as sensations, actions, thoughts,
and emotions (Bear, Connors & Paradiso. 1996). During a seizure, the firing of neurons may occur as often as 500 times a second (National Institute of Neurological Disorders and Stroke [NINDS], 2004). This is far greater than the normal functional rate of approximately 80 times a second (NINDS, 2004). External triggers for seizures include stimuli such as flashing lights and sounds. Internal triggers can include psychological or physical stress, sleep deprivation, or hormonal changes (Lowenstein, 2004). Many seizures occur with no apparent stimulus. A seizure may be localized to a small area of the brain, or it may spread to other brain regions. If the abnormal discharges remain localized, clinical symptoms may not be detectable except for EEG abnormalities. If the seizure spreads to include larger areas of the brain, clinical symptoms and EEG manifestations will become apparent.

The diagnosis of epilepsy is established if the patient has two or more occurrences of unprovoked seizure activity (Lowenstein, 2004). Unprovoked seizures occur in the absence of conditions typically known to induce seizure activity, such as stroke, closed head injury, meningitis, overdose of certain medications or drugs, low blood sugar, or low sodium in the blood. A precise diagnosis of epilepsy can be made only after considering all the relevant data, including seizure type, signs and symptoms of the disorder, electroencephalogram (EEG), age of seizure onset, family history, imaging studies, cause, and precipitating factors, as well as additional pertinent information. (Benbadis, 2001).

Epilepsy is not a single illness, but a variety of disorders that reflect underlying brain dysfunction of differing etiologies (Fisher et al., 2005). Dodrill (1992) described the epilepsies as “a basket of related disorders” with their own related features, such as
underlying brain dysfunction, seizure effects, EEG patterns, and impact of antiepileptic drugs.

**Incidence of epilepsy.** There are approximately 200,000 new cases of epilepsy diagnosed in the United States each year (Epilepsy Foundation of America, 2009). Males are slightly more likely to develop epilepsy than females. The incidence of epilepsy is highest in children under 2 years of age and in the elderly over 65 years. By age 20, 1% of the population is likely to have developed epilepsy. By 75 years of age, it is expected that 3% of the population will have been diagnosed with epilepsy, and 10% will have experienced some type of seizure.

**Prevalence of epilepsy.** It is estimated that epilepsy affects between 2.7 to 4 million people, or approximately 1% of the U.S. population. In view of the fact that 75% of people with epilepsy have their first seizure before the age of 20, the effect on a large number of people over a major portion of their lives cannot be minimized (Smith, 1987).

**Causes.** Epilepsy is a disorder with many possible causes. Anything that disturbs the normal pattern of neuron activity, including neurological illness, traumatic brain injury, and abnormal brain development can lead to seizures. During the neonatal period and early infancy, potential causes include developmental abnormalities, genetic disorders, infections and metabolic disturbances. The most common type of seizures in late infancy and early childhood are febrile seizures. These are seizures associated with fevers but without central nervous system infection or other defined evidence of cause, with an overall prevalence of 3-5% (Lowenstein, 2004). In adolescents and young adults, trauma, infection, brain tumors, and illicit drug use are the most common causes. In older adults, epileptic seizures are commonly induced by cerebrovascular disease, brain
tumors, alcohol withdrawal, degenerative CNS diseases, and metabolic disorders. In more than half of all epileptic patients, no cause can be found (American Association of Neurological Surgeons [AANS], 1998).

**Treatment.** There are a variety of treatments for epilepsy, including drug therapy, surgery, vagus nerve stimulation, biofeedback, and a ketogenic diet. A ketogenic diet consists of a high fat and low carbohydrate intake and is thought to help stabilize neurons exposed to seizures (AANS, 1998; Emory University Health Sciences Center, 2005). Of these, drug therapy remains the most widely used form of treatment. For about 80% of individuals diagnosed with epilepsy, seizures can be controlled with medication, but approximately 20% of epilepsy patients do not respond to any treatment.

If antiepileptic drug therapy fails, brain surgery and removal of the seizure focus is usually considered. Among patients with partial seizures, the area of the brain that triggers the seizures is removed. These areas are more easily identified with improved technology. Following surgery, some patients will be seizure-free, while others will have fewer or more controlled seizures.

**Seizure presentation.** The manner in which a seizure presents depends upon a variety of factors. The location of onset in the brain is of major importance. Patterns of propagation, medications, brain maturity, confounding disease processes, and sleep-wake cycle are also intrinsic as to how the seizure manifests (Fisher et al., 2005).

A feeling of unease or discomfort, called an aura, may precede an epileptic attack, thereby serving as a warning of the onset of a seizure. Another sign of an impending epileptic seizure may include a visual phenomenon such as flickering lights or “sunbursts”. Increased risks for seizures are stress, sleep deprivation, fatigue, insufficient
food intake, flashing lights or failure to take prescribed anti-convulsant medication (AANS, 1998).

Another manner in which seizure activity affects the brain is by cognitive impairment. Deficits often appear as problems with attention, perception, or memory. Memory difficulties can manifest as interruption of memory formation or retrieval. Conversely, they can appear as intrusions of inappropriate memories, such as those that elicit déjà vu or other forced memories (Fisher et al., 2005). Cognitive deficits can also appear as motor or speech difficulties, or as problems with execution of behaviors. In addition, they can present as emotional disturbances. The specific expression of the deficits is indicative of the location of the epileptogenic zone.

Epileptic seizures are but one sign or symptom of an epileptic disorder. Once epileptic seizures are diagnosed, the next step is to determine the epileptic syndrome.

1.1.2 Epileptic syndromes.

A syndrome is a cluster of symptoms and signs that occur together but may not have a single known cause or pathology. Epilepsy syndromes usually involve a common underlying mechanism and include epileptic seizures as the principal feature (Lowenstein, 2004). Epilepsy syndromes are determined by many factors, including type of seizures, age of seizure onset, family history of seizures, physical examination, neurologic imaging studies, and electroencephalography (EEG) findings (Shneker & Fountain, 2003).

1.2 Classification of Seizure Disorders

In 1970, a seizure classification system was suggested by the International League Against Epilepsy (ILAE; Gastaut, 1970). It has since been revised and accepted as The
International Classification of Epileptic Seizures (ICES) (Commission on Classification and Terminology of the International League Against Epilepsy, 1981). Although there are several methods by which seizures can be classified, the most practical classification is based on the area of the brain in which the seizure originates. The ILAE classification system takes into consideration the clinical features and EEG findings associated with the seizures (Appendix A).

The main feature that distinguishes the different categories of seizures is whether the seizure activity is partial or generalized. Not all seizure types can be classified into these two categories. A third classification, unclassified seizures, has been included to cover the seizure types that do not fit into the two main categories. These occur most often in infants with immature central nervous systems (Lowenstein, 2004). Partial seizures are often associated with structural abnormalities of the brain. In contrast, generalized seizures may result from cellular, biochemical, or structural abnormalities that have a more widespread distribution (Lowenstein, 2004).

1.2.1 Partial seizures.

Partial seizures occur within discrete areas of the brain, and the initial clinical and EEG manifestations appear to arise from an anatomical region limited to part of one cerebral hemisphere. Partial seizures are sub-divided into three categories: simple, complex, and secondarily generalized. Simple and complex partial seizures can be differentiated by the presence or absence of conscious awareness. Simple partial seizures are characterized by motor, sensory, autonomic and/or psychic symptoms without impairment of consciousness. Complex partial seizures may also involve the same type of motor, sensory, autonomic, and/or psychic symptoms, but include automatisms and
demonstrate a disturbance of consciousness. Automatisms are involuntary, automatic behaviors which range from minor activities, such as lip smacking, tooth grinding, swallowing, fumbling, and tapping, to more complicated behaviors, such as exhibiting emotional facial expressions and vocal or verbal utterances. The fact that complex partial seizures involve loss of consciousness implies that epileptogenesis occurs in centers of higher cortical functioning.

Seizures that begin as partial seizures, but spread diffusely to other brain areas, are termed partial seizures with secondary generalization. These seizure types are usually with tonic-clonic, tonic, or clonic symptomatology and ictal EEG discharges becoming rapidly generalized over the cerebral cortex. A partial seizure with secondary generalization is often difficult to distinguish from a primarily generalized tonic-clonic seizure; however, distinguishing between the two seizure types is extremely important in terms of treatment and clinical implications.

1.2.2 Generalized seizures.

Generalized seizures are characterized by the simultaneous onset of seizure activity in both cerebral hemispheres, and typically involve some disturbance of consciousness. Initial clinical and EEG changes are indicative of bilateral involvement from the start. Generalized seizures include several sub-types, such as absence seizures; tonic, clonic, and tonic-clonic seizures; myoclonic seizures; and atonic seizures.

Absence seizures typically involve sudden but brief lapses of consciousness. Consciousness returns as rapidly as it was lost, and often the individual is not even aware of the occurrence of the seizure. Activity continues as though it had not been interrupted and there is usually no postictal confusion. Absence seizures may produce symptoms
that range from mild clonic symptoms, atonicity, automatisms, and/or tonic components associated with typical absence seizures, to impaired consciousness and motor symptoms of tonic-clonic seizures associated with atypical absence seizures. Other generalized seizures can involve loss of postural muscle tone (atonic “drop attacks”) with brief loss of consciousness but no postictal confusion, or myoclonus (sudden and brief muscle contraction) to all or part of the body.

1.3 Classification of Epileptic Syndromes

Classification of seizure types is important, as it provides identification of the region of ictal onset and guides initial diagnostic testing (Shneker & Fountain, 2003). It also facilitates treatment planning and establishing a prognosis (Lowenstein, 2004). Classification of syndromes is also important because when a syndrome is identified, insight into various aspects of the syndrome, such as prognostic and diagnostic factors, is possible. In addition, communication between health care professionals can more easily be facilitated (Shneker & Fountain, 2003).

Previous classification systems identified seizures based on seizure semiology and EEG findings. More recently (1989), a classification scheme was proposed by the ILAE that categorized epileptic syndromes according to etiologies and EEG patterns. The epileptic syndromes are divided primarily into two broad categories: generalized epilepsies and focal epilepsies (Chang & Lowenstein, 2003). The primary distinction is that the generalized epilepsies have generalized epileptiform abnormalities on EEG and focal epilepsies have focal abnormalities on EEG (Nair, 2003). Many forms of generalized epilepsy have a likely genetic origin. Most partial epilepsies are thought to be the result of central nervous system insults, but often, the nature of the insult is never
identified (Chang & Lowenstein, 2003). In the revised classification system, the epileptic syndromes are then further sub-divided into idiopathic (unknown cause), symptomatic (identifiable cause) or cryptogenic (hidden cause) etiologies depending on whether the seizures have a focal or generalized EEG onset (Appendix B). Identification of the epilepsy syndrome is important, as it contributes to the understanding of a patient’s history and facilitates the development of a prognosis. Clarity can also be placed on the type of treatment and therapeutic options. Diagnosis of epilepsy depends on knowledge of the different syndromes and their clinical and laboratory manifestations (Panayiotopoulos, 2002). After seizure semiology, EEG characteristics, age of onset, and evidence of brain pathology have been determined, many focal seizures may be classified into one of the epilepsy syndromes based upon where in the brain the seizures originate.

Symptomatic, focal onset seizures are those epilepsies that have an identifiable cause. Common causes of symptomatic pathology include brain trauma, tumors, strokes, or infections (Chang & Lowenstein, 2003). Mesial temporal lobe epilepsy is a focal onset, symptomatic syndrome and is considered one of the most prevalent epileptic syndromes.

1.4 Temporal Lobe Epilepsy

Temporal lobe epilepsy (TLE) was defined by the International League Against Epilepsy as a condition characterized by recurrent unprovoked seizures originating from the medial or lateral temporal lobe (Wieser, Hajek, Gooss & Aguzzi, 2001). It is the most common of the localized epilepsies. The seizures associated with TLE consist of simple partial seizures without loss of awareness, or complex partial seizures, with loss of awareness.
Confusion exists as to the precise meaning of temporal lobe epilepsy because it has been inappropriately used to refer to conditions where the primary epileptogenic focus is outside the temporal lobe, with discharges propagating from that region to the temporal lobe resulting in complex partial type seizures (Wieser et al., 2001). An important distinction should be made here because the site of seizure onset, according to the ILAE description, defines the type of epilepsy, and therefore, the related clinical manifestations.

In temporal lobe epilepsy both simple partial and complex partial seizures can be found, but it is important to distinguish between limbic partial seizures and neocortical partial seizures, although their semiology does overlap in many respects (Wieser et al., 2001). Hippocampal sclerosis (HS) is the most common pathological feature of temporal lobe epilepsy, and TLE associated with HS represents a distinctive epileptic syndrome (MTLE) (Chang & Lowenstein, 2003). The diagnosis of MTLE is based on etiology, seizure history, clinical presentation, progressive nature, intractability, histopathologic examinations, and imaging results. All of these features must be considered in order for the proper diagnosis and treatment to be achieved (Wieser et al., 2001).

TLE is currently sub-divided into two distinct types according to the areas associated with the disease: lateral (neocortical) temporal lobe epilepsy and medial temporal lobe epilepsy.

1.4.1 Lateral temporal lobe epilepsy.

Lateral, or neocortical, temporal lobe epilepsy simply involves epileptogenesis arising from the neocortical temporal lobe. The neocortex includes the superior, middle, and inferior temporal gyri. Localization of the epileptogenic zone by surface EEG is less
reliable for neocortical epilepsy than for mesial temporal epilepsy, as discharges can be absent on surface EEG when the focus is deep (Benbadis, 2001). In addition, [18F]-fluorodeoxyglucose positron emission tomography (FDG PET) may also be difficult to use to differentiate mesial from lateral temporal neocortical foci (Kim, Yi, Son, & Kim, 2003). Seizures do not commonly originate in the lateral neocortical temporal lobe cortex and occur less often than seizures originating in the MTL structures. It is said that fewer than 10% of patients prone to temporal lobe seizures have the seizures arising from temporal lobe neocortex (Williamson, Engel, & Munari, 1998). When they do occur, a structural lesion is often the cause and may involve the lateral temporal cortex only, or may include the insula. Seizures originating from the lateral cortex have often been found to spread to the ipsilateral mesial temporal structures. Wieser et al. (2001, p. 137) suggested that the mesial structures might serve as a kind of “amplifier” that facilitates the duration and continuation of seizure discharges. Signs and symptoms of lateral temporal lobe epilepsy do not clearly differ from those of medial temporal lobe epilepsy; however, epileptic discharges often arise from more than one lobe in lateral temporal epilepsy (Oxbury & Duchowny, 2001). Although there is no semiology specific to lateral temporal seizures, typically, ictal aphasia, hallucinations (auditory, vestibular, or visual), and motor symptoms with contralateral tonic-clonic manifestations and head-eye deviation occur (Wieser et al., 2001). A feeling of vertigo and déjà vu may be more common with neocortical temporal lobe epilepsy, and an abdominal aura may be more often associated with mesial temporal lobe epilepsy (Oxbury & Duchowny, 2001).

1.4.2 Mesial temporal lobe epilepsy.
Mesial temporal lobe epilepsy is a term frequently used when referring to seizures that arise from mesial temporal lobe structures, but more often, when referring to the syndrome of epilepsy that arises as a consequence of mesial temporal sclerosis (Oxbury & Duchowny, 2001). The primary features of the mesial temporal lobe epilepsy syndrome are: seizure onset in mesial temporal structures such as the hippocampus, amygdala and adjacent parahippocampal cortex, hippocampal sclerosis, auras (epigastric and psychic), automatisms (i.e., lip-smacking, finger-rubbing), EEG abnormality, focal functional deficits, and typical lifetime pattern of non-response to medications (Benbadis, 2001; Paradiso, Hermann, & Robinson, 1995). It can be characterized in terms of genetic and environmental factors, natural history, pathogenesis, and prognosis, but hippocampal sclerosis (HS) is its most important association (Engel, Williamson, & Wieser, 1997).

The syndrome of MTLE is often resistant to antiepileptic drugs, but responds well to surgical intervention. The term mesial temporal sclerosis is sometimes referred to as Ammon’s horn sclerosis, and more commonly, hippocampal sclerosis, named after its most common pathologic substrate (Oxbury, 2001). Hippocampal sclerosis involves a specific type of cell loss that consists of severe depletion of hippocampal neurons with gliosis, particularly in the CA1 and CA3-CA5 zones, and of the dentate granule cells (Oxbury, 2001; Wieser et al., 2001). Wieser and colleagues (2001) point out that the cell loss in the CA2 region is often spared. In addition, several structures, including the subicular complex, entorhinal cortex, other transitional cortex, and the temporal gyri are fairly resistant to cell loss. Neuronal cell loss and gliosis characterize mesial temporal lobe epilepsy. Hippocampal sclerosis is very often a bilateral condition, but the majority of epileptogenic activity tends to focus on one side (Engel et al., 1997). While the exact
cause of hippocampal sclerosis is not known, and a matter of much debate, it is certain
that depletion of specific hippocampal neurons and synaptic reorganization are
responsible for its epileptogenicity (Engel et al., 1997). However, not every damaged
hippocampus is epileptogenic and not every person with severe epilepsy has hippocampal
sclerosis.

The mesial temporal lobe consists of the hippocampus, amygdala, and
parahippocampal region. Declarative memory depends on the functional integrity of the
hippocampus and parahippocampal regions (Jokeit, Okujava, & Woermann, 2001).

**Incidence and prevalence of MTLE.** MTLE is considered to be the most
common human epileptic syndrome. About 40-50% of newly diagnosed cases have
partial seizures, most often complex partial seizures (Wieser et al., 2001). It is well
known that patients with MTLE experience a high rate of failure with antiepileptic drug
treatment, but find surgical remedies quite successful.

**Genetics and pathophysiology.** Childhood febrile seizures, especially when
prolonged, have been implicated as one important factor in the development of TLE
associated with MTS, although this issue does remain controversial. An association
between a history of childhood febrile seizures and hippocampal sclerosis has been
established, but the explanation is uncertain (Wieser et al., 2001). Nevertheless, the
prevalence of a family history of febrile convulsions is higher in patients with late seizure
recurrence and in patients with temporal lobe epilepsy treated surgically (Wieser et al.,
2001).

**The seizures of MTLE.** Habitual seizures usually begin earlier for MTLE with
hippocampal sclerosis (HS) than for MTLE with other lesions (Wieser, 2004). Studies
have demonstrated that the “initial precipitating incidents” (IPIs), including febrile seizures, trauma, hypoxia, and intracranial infection, often, but not always, occur before the age of 5 years, with the majority of seizures beginning between 4-16 years of age (Wieser, 2004).

**Seizure propagation.** Seizure spread is slow in MTLE with HS in comparison with seizures located in other areas of the brain. According to Wieser (2004) seizure spread follows preferred propagation pathways that usually reflect connected brain regions. The mode of propagation cross hemispheres is not entirely clear; once seizure activity has spread to the ipsilateral frontal lobe, the propagation pattern may become contralateral. Without involvement of the ipsilateral neocortical TL, spread to the ipsilateral neocortical TL might be seen as often as spread to the contralateral mesial TL structures. Very often ipsilateral frontal or orbitofrontal cortices are involved ictally. Some evidence exists that ipsilateral frontal or orbitofrontal ictal involvement is not a necessary condition for seizure spread to the contralateral mesial temporal lobes (Wieser, 2004).

1.5 **Assessment of Cognitive Functioning**

It is important to understand the measures of cognitive function and their associations with the individual brain regions in temporal lobe epilepsy. It is also useful to explore the effects of localization in relation to cognitive function. Surgical outcome and comparisons made with pre-surgical data provide valuable information for determining cognitive status and level of dysfunction in patients with TLE.
1.5.1 Intellectual assessment of TLE.

Intellectual assessment in patients with temporal lobe epilepsy has become a standard component in the overall neuropsychological evaluation of cognition. The Wechsler intelligence scales have been the most frequently used psychological tests in the United States (Giordani et al., 1993). These include the Wechsler Adult Intelligence Scales (WAIS, WAIS-R, WAIS-III), and the Wechsler Intelligence Scale for Children (WISC, WISC-R, WISC-III). Measures of general intelligence are routinely administered prior to and following surgery even though they are not believed to be the most sensitive indices of temporal lobe functioning (Dodrill, Hermann, Rausch, Chelune, & Oxbury, 1993). The necessity of including intellectual assessment in neuropsychological batteries is somewhat controversial. According to Helmstaedter (2004), the intelligence quotient (IQ) does not necessarily add information to standard neuropsychological test results. Conversely, Jones-Gotman, Smith and Zatorre (1993) find IQ data useful, as it is standardized on a large population, is valuable for evaluating patient’s abilities globally, and allows for comparisons of pre- to postoperative results. In children, IQ testing is important, as it is reflective of cognitive development. IQ tests are also important in the planning of educational interventions and rehabilitation for the various epilepsy populations (Giordani et al., 1993). Additionally, they provide a basis from which other neuropsychological tests can be compared.

The WAIS and other intelligence tests were not originally designed for neuropsychological assessment, but the WAIS subtests reflect abilities associated with various cognitive domains (Alpherts et al., 2004). Several of their subtests are especially
sensitive to deficits in memory processes (e.g., Vocabulary or Information) and visual-
motor ability (e.g., Block Design or Object Assembly) (Giordani et al., 1993).

It has been shown that anatomical location of seizure focus differentiates patient
groups by type of intellectual deficit (Giordani et al., 1993). Lower scores for individuals
with temporal lobe abnormalities in comparison with other patients groups or controls
have been reported for Wechsler Adult Intelligent Scale (WAIS) Verbal IQ, Picture
Arrangement, Information, and Vocabulary (Giordani et al., 1993). Patients with
generalized seizures tended to perform worse on Similarities. This was attributed to
recall deficits in the temporal lobe group as opposed to deficits of abstraction abilities in
the generalized seizure group. Giordani et al. (1993) suggested that patients with
temporal lobe abnormalities exhibit deficits on recall and memory tasks, while patients
with generalized seizures demonstrate deficits in attention or visuospatial processes, seen
on specific subtests such as Digit span, Block Design or Object Assembly.

The ILEA Commission Report (Weiser, 2004) determined that in general, mesial
temporal lobe epilepsy (MTLE) with hippocampal sclerosis can be associated with
general intellectual impairment. While many studies have emphasized the importance of
memory deficits in MTLE, Hermann, Seidenberg, Schoenfeld and Davies (1997) found
that deficits in MTLE are not limited to the learning-memory domain but extend to other
cognitive functions, including intelligence.

**Localization and lateralization of intelligence.** Previous studies found Verbal-
Performance IQ score differences to be of limited utility in localizing and lateralizing
lesions in TLE (Jones-Gotman et al., 1993). In addition, in a study examining pre and
postoperative IQ test scores, Jones-Gotman et al. (1993) found no significant differences between left and right hemisphere seizure focus groups.

**Preoperative and postoperative effects on intelligence.** Studies comparing pre- and post-operative effects on IQ demonstrated that patients undergoing anterior temporal lobectomies (ATLs) may be expected to show some modest increase in their intelligence scores (Dodrill et al., 1993). Caution should be noted when comparing pre- to postoperative performance, as increments of improvement have been correlated with practice effects seen with nonsurgical seizure patients (Dodrill et al., 1993; Jones-Gotman et al., 1993). Alpherts et al. (2004) studied the long-term (up to 6 years) effects of anterior temporal lobectomies on intelligence. Results indicated that both VIQ and PIQ increased over the six-year period. The PIQ increased to a greater extent than the VIQ. Patients with left temporal lobectomies exhibited a slightly greater increase in FSIQ points than right temporal lobectomy patients. Left temporal lobectomy patients gained 3.6 VIQ, 10.3 PIQ, and 7.4 FSIQ points over the 6-year period. Right temporal lobe patients gained 2.9 VIQ, 7.7 PIQ, and 5.5 FSIQ points over 6 years (Alpherts et al., 2004).

**Risk factors of intellectual impairment.** Overall, the literature suggests that seizure disorders are associated with an increased likelihood of intellectual problems (Dodrill, 1992). There are a variety of potential risk factors that contribute to these findings. In addition to the significant contributions of non-neurological social and familial factors to IQ, the two most common predictor variables of intellectual compromise in epilepsy are early age at onset of regular seizures and duration of seizures (Dodrill, 1992; Glosser, Cole, French & Saykin, 1997; Jokeit & Ebner, 2002; Perrine, Gershengorn, & Brown, 1991; Warmflash, 1997; Wieser, 2004).
Early onset of seizures appears to be one of the strongest predictors of intellectual impairment. Dodrill (1992) noted that, in general, the earlier in life epilepsy appears, the lower the mental abilities. Regularly occurring seizures experienced during a critical period of brain development in early childhood poses the greatest risk to cognitive development in epilepsy patients (Glosser et al., 1997). In a study of 410 adults with epilepsy, Dodrill (1992) found a steady decrease in WAIS Full Scale IQ scores that positively correlated with age at seizure onset. FSIQ scores steadily increased from 90.6 in patients with age at onset of 0-5 years, to 100.76 in patients with age at onset of 19-28 years.

Duration of seizure activity can also prove to be a detriment to intellectual growth (Jokeit & Ebner, 1999, 2002). A longer duration of seizure disorder can be associated with diminished mental abilities (Dodrill, 1992). According to Oyegbile, Dow et al. (2004), the duration of epilepsy is not a single factor, but rather, reflects the influence of several factors acting alone or in combination. Oyegbile, Dow, and colleagues (2004) suggested that the longer an individual suffers from epilepsy, the greater the possibility of exposure to conditions that can cause seizure-induced neuronal damage, such as subclinical epileptiform discharges during interictal periods, and the possibility of secondary seizures. As duration of epilepsy increases, the exposure to antiepileptic medications also increases, as does the risk of seizure-related accidents including closed head injury (Jokeit & Ebner, 1999; Oyegbile, Dow et al., 2004). Jokeit & Ebner (1999) found that patients with greater than 30 years of temporal lobe epilepsy performed significantly worse than patients with 15 to 30 years of epilepsy. In a later study, Jokeit
& Ebner (2002) found that chronic epilepsy exceeding two decades was associated with greater cognitive dysfunction.

Other associated factors that impact intellectual outcome are frequency of seizures and education level. While Perrine and colleagues (1991) found that a high frequency of seizures can produce intellectual dysfunction, Dodrill (1992) noted that the association between more frequent seizures and diminished mental abilities had not been clearly demonstrated. Factors such as the extent of seizure history being examined and the impact of seizure types may contribute to the explanation for this discrepancy.

Another factor that has been shown to modify the effects of cerebral insults is education. Education and IQ scores are moderately correlated. Oyegbile, Dow et al. (2004) found that the greater the level of education a patient had acquired, the greater the capacity to withstand the neurological insults associated with epilepsy and its treatment. Oyegbile, Dow et al. (2004) also suggested the possibility that subjects who attain a higher level of educational or occupational achievement, or who participate in mentally stimulating activities may benefit from increased plasticity that may serve to delay or minimize disease effects. This is the theory of cognitive reserve which states that “cognition holds steady until a certain threshold of disease progression is reached, beyond which cognition then begins to decline” (Sawrie et al., 2000, p. 106).

Theoretically, a higher education level extends the cognitive threshold and creates a protective effect, limiting the influence of duration and frequency of seizure activity. A study by Jokeit & Ebner (1999) supported this theory. The mean full scale IQ (FSIQ) was stable for a longer duration of temporal lobe epilepsy in patients with higher educational attainment than in less educated patients (Jokeit & Ebner, 1999). In her
investigations of intellectual functioning in epilepsy, Warmflash (1997) found that seizure-related variables, such as age of seizure onset, duration of epilepsy, hemisphere of seizure focus, gender, and education accounted for a small portion of the variance in intellectual functioning. A much larger amount of the variance was accounted for by the secondary consequences of those factors on educational attainment. Therefore, early diagnosis and treatment of epilepsy is important to ensure continuous, uninterrupted education.

1.5.2 Neuropsychological assessment and measures of TLE.

Patients with epilepsy are known to have impaired cognitive performance compared to a matched sample of healthy subjects (Meador, 2002). A significant amount of research exists with regard to the type of cognitive impairment in epilepsy, and slowing on speeded tasks, memory impairment, and attentional and concentration difficulties are the most frequently associated with epilepsy (Aldenkamp, Baker, & Meador, 2004). Because the brain is the basis for mental abilities, disruptions may cause alterations in brain functions (Dodrill, 1992). Disruption of these functions can have severe consequences on cognition and behavior that can often be more harmful than the seizures themselves (Aldenkamp et al., 2004). One of the major consequences is the impairment of cognitive function. Neuropsychological assessment is a method of pinpointing cognitive dysfunction by utilizing a variety of tests sensitive to individual cognitive domains. It works by placing demands on individual cerebral systems in order that a pattern of strengths and weaknesses may be obtained which will point to area(s) of dysfunction (Jones-Gotman et al., 1993). Neuropsychological testing covers a broad range of abilities, including problem solving, communication, memorization, and
attention/concentration. Tests should be chosen and administered that are sensitive to function in either the dominant or non-dominant hemisphere and in various areas within each hemisphere (Jones-Gotman et al., 1993).

Interpretation of results from each test should take place in the context of all other tests in the neuropsychological battery. A pattern of specific deficits should then emerge on the performance of some tasks relative to others. That pattern is usually associated with a set of brain areas that mediate the dysfunction (Jones-Gotman, 1991). In epilepsy, neuropsychological assessment provides a systematic method for evaluating and treating the social, emotional and physical consequences of epilepsy (Dodrill et al., 1993).

It is important to test a wide variety of cognitive abilities and to compare and contrast the many facets of each cognitive domain. Inclusion of tests sensitive to function in frontal, parietal, and posterior temporal cortex is important. The most commonly employed method of neuropsychological assessment consists of the use of an established and validated group of neuropsychological tests (Dodrill, 2004). In testing patients with epilepsy, one should be certain that areas of importance in epilepsy are covered adequately, including the effects of antiepileptic drugs and interictal EEG abnormalities. Often, emotional and psychosocial functioning is disrupted in epilepsy and should therefore be included in the assessment measures (Dodrill et al., 1993). One of the most crucial aspects of the neuropsychological evaluation is the assessment of memory due to the prominent role of the temporal lobes in epileptogenesis (Jones-Gotman, 1991). Tests selected to assess all aspects of learning and memory, as well as those sensitive to hippocampal function, (i.e., immediate and delayed recall, recognition) are essential to include (Jones-Gotman, 1991; Jones-Gotman et al., 1993). Helmstaedter
(2004) recommended that functions particularly sensitive to the negative side effects of AEDs be evaluated, such as episodic memory, executive functions, language (fluency), attention, visuoconstruction, and psychomotor speed. In this way, areas of dysfunction can be localized, and by including verbal and nonverbal functions, cognitive impairment may also be lateralized.

Influences of cognitive compromise. The cognitive sequelae of epilepsy are associated with the seizure type and location; however, cognition in epilepsy is influenced by many variables. These variables include cerebral lesions acquired prior to seizure onset, hereditary background, psychosocial influences, etiology, age at seizure onset, type, frequency, and duration of seizures, structural cerebral damage caused by prolonged or repetitive seizures; duration of epilepsy; anti-epileptic drugs; and the nature and location of the underlying pathology (Meador, 2002; Oxbury, 2001). In focal epilepsy, the nature and location of the underlying pathology are key factors, as they determine which cognitive functions are compromised; however, all the other factors contribute to the extent and severity of neuropsychological functioning (Oxbury, 2001). Additionally, it is well known that epileptic seizures disrupt brain function during epileptic events, but furthermore, the dysfunction continues to exist between seizures in many individuals with epilepsy (Dodrill, 1992). Consequently, dysfunction caused by ictal events may be compounded by interictal activity that is often undiagnosed. Although the exact cause of cognitive impairment in epilepsy has not been fully explored, it is clear that at least three factors are involved: etiology, the seizures, and the side effects of treatment. In general, an early age at onset, along with greater seizure
frequency, duration, and severity, results in a greater likelihood of impaired cognition (Meador, 2002).

**Duration of epilepsy.** In their research, Oyegbile, Dow et al. (2004) found that the degree of cognitive morbidity was significantly associated with the duration of epilepsy. Abnormal test scores increased proportionately with an increasing duration of epilepsy. This relationship remained after controlling for many other variables (Oyegbile, Dow et al., 2004).

**Years of education.** Oyegbile, Dow, and associates (2004) also reported that patients with fewer years of education exhibited a stronger association between the duration of epilepsy and decline in cognitive functioning. As previously noted, it has been suggested that patients with epilepsy with more years of education (i.e., cognitive reserve) are less likely to succumb to the damaging cognitive deficits associated with epilepsy and its treatment.

**Age of onset.** Early age at onset of epilepsy has been associated with cognitive impairment. Hermann et al. (1997) found that early age at onset of epilepsy, particularly in temporal lobe epilepsy, is associated with generalized impairment of cognitive-intellectual functioning. There are several possible reasons for this, but possibly the most significant is the long-term impact of seizures during a person’s developmental years. Diminished educational attainment, risk of damage over time, the adverse effect of seizures over time, and anti-epileptic drug use are additional factors that adversely effect cognitive integrity (Dodrill, 1992). Davies et al. (1996) also found a significant correlation between severity of hippocampal sclerosis and age of onset of epilepsy.
Many patients with early onset TLE develop right hemisphere language dominance (13-15%) which is rare in the normal population (1-2%) (Rausch, Boone & Ary, 1991).

*Anti-epileptic drugs (AEDs).* AEDs are just one of the many factors that can affect cognition in patients with epilepsy. Anti-epileptic drug therapy is the major form of treatment for most patients with epilepsy (Meador, 2002). The overall goal is to completely prevent seizures without causing any adverse side effects (Lowenstein, 2004). AEDs reduce the neuronal irritability associated with epileptic seizures, but by doing so, they may also impair neuronal excitability (Meador, 2002). This creates an adverse effect on cognition. The major cognitive effects of AEDs are impaired attention, vigilance, and psychomotor speed (Meador, 2002). The degree to which deficits are experienced depends upon several factors including the type and dosage of AED used. Poly-pharmacy, higher AED dosages, and higher anticonvulsant blood levels increase the risk for cognitive side effects (Meador, 2002). Memory tests with a high vigilance load are more sensitive to AED effects. The modest magnitude of AED effects might be clinically significant under certain circumstances (e.g., during brain development or in situations that require vigilance or learning). The adverse cognitive effects of AEDs are offset in part by reduced seizures.

*Surgical assessment of epilepsy.* A subspecialty of neuropsychology is the evaluation of epileptic patients being considered for surgical intervention (Jones-Gotman et al., 1993). Pre-surgical evaluation is designed to ascertain the functional and structural basis of the patient’s seizure disorder (Lowenstein, 2004). The primary objective is to determine the site of cerebral dysfunction and to establish a baseline from which postoperative changes in cognition can be identified. In epilepsy surgery
neuropsychological evaluation is not a single cognitive status examination, but a repeated
measure with one or more post-operative follow-up evaluations (Helmstaedter, 2004).

Localizing dysfunction and lateralization of language dominance are critical
aspects of neuropsychological assessment. Dodrill et al. (1993) found that localization of
findings to the temporal lobes was more likely to be associated with a good surgical
outcome (58%) than with a poor outcome (31%). This is most likely due to the fact that
patients with MTLE are typically refractory to anticonvulsants, but respond extremely
well to surgical intervention (Lowenstein, 2004).

**WADA test.** Cerebral dominance is necessary to establish when considering
surgery in order to minimize risk of severe cognitive deficits to language and memory
functions. One method of determining cerebral dominance is the intracarotid amobarbital
test (IAT), also known as the WADA. Andelman, Neufeld, and Fried (2004) noted that
the WADA is useful for not only determining cerebral speech dominance, but also for
predicting post-surgical amnesia and laterality of seizure focus. Prior to temporal lobe
surgery, patients typically undergo WADA testing. Sodium amobarbital is administered
to the left or right carotid artery to produce temporary unilateral hemispheric dysfunction.
While the hemisphere is temporarily inactive, language and memory tests are given and
the effects of the proposed surgery on language and memory processes can be assessed
(Loring, Meador, & Lee, 1992). Left hemisphere language dominance is usually found in
approximately 90% of right-handed patients with temporal lobe epilepsy (Oxbury, 2001;
Strauss et al., 1995). This is slightly less than the normal population (97%), suggesting
the possibility that temporal lobe epilepsy, or a related factor, interferes with the normal
development of language lateralization (Oxbury, 2001). While the WADA was
originally developed to determine language lateralization, it was subsequently extended to predict severe amnesia after surgery for temporal lobe epilepsy (Wieser et al., 2001). Its usefulness in memory assessment, however, remains controversial. Studies have shown that although the frontal, parietal, and lateral temporal structures receive the injected sodium amobarbital, it does not reach the hippocampal and medial temporal regions (de Silva et al., 1999). Ries et al. (2004) suggest that functional magnetic resonance imaging (fMRI) offers a less invasive alternative to the WADA procedure and is equally as effective. The fMRI procedure does not rely on vascular transmission to reach cerebral destinations; rather it uses blood oxygenation level-dependent response to measure neuronal activity in temporal lobe regions (Jokeit et al., 2001). Rabin et al. (2004) found that temporal lobe epilepsy patients showed asymmetrical activation in the hippocampal and mesial temporal region during an fMRI investigation of memory lateralization that correlated significantly with memory lateralization using WADA testing (Rabin et al., 2004). Although studies investigating the use of fMRI for pre-surgical lateralization of memory function are promising, this technique alone cannot be used to assess the risk of post-surgical amnesic syndrome with confidence (Baxendale, 2002). The two techniques in combination may provide useful data that results in improved prediction of post-surgical verbal memory dysfunction (Ries et al., 2004).

**Prediction of surgical outcome.** During the preoperative evaluation for epilepsy surgery it is necessary to assess mesial temporal lobe function in order to successfully predict postoperative memory deficits and lateralize seizures (Detre et al., 1998).

The question has been raised as to whether pre-surgical assessment can be used as a predictor of seizure relief following surgery (Dodrill et al., 1993). Wannamaker and
Matthews (1976) demonstrated that an overall measure of neuropsychological impairment might be able to predict seizure relief after surgery. They suggested that persons less impaired pre-surgically had the best prognosis. Dodrill et al. (1993) stated that overall measures of cognition were of limited use in terms of predicting outcome. Of all the measures studied, scores on WAIS Digit Symbol, Marching Test preferred hand, and two measures of adjustment (MMPI Hysteria scale and Paranoia scale) were found to be predictive of seizure relief (Dodrill et al., 1993). The percentage of patients correctly classified was 71% (Digit Symbol), 72% (Marching Test), and 75% (MMPI scales).

The objective of epilepsy surgery is to stop seizures by removing dysfunctional tissue. Successful surgery can prevent further cognitive decline caused by chronic epilepsy and may even improve cognition by facilitating the need for fewer AEDs or lower dosages of them (Meador, 2002). It can also improve cognition by releasing functions that were secondarily affected prior to surgery (Helmstaedter, 2004).

The success of temporal lobectomy for treatment of intractable temporal lobe epilepsy is well established (Graydon, Nunn, Polkey, & Morris, 2001). Post-operative cognitive deficits frequently occur, however, and typically involve language or verbal memory functions (Meador, 2002). Risks factors for cognitive deficits following temporal lobectomy include: resection of the language dominant hemisphere, absence of atrophy/gliosis in the hippocampus or mesial temporal lobe structures on the side of resection, MTL sclerosis contralateral to the side of resection, and later age of epilepsy onset (Dodrill et al., 1993; Meador, 2002). The extent of post-operative cognitive decline is difficult to predict, as many factors, such as the previously mentioned risk factors, play a role in determining the outcome. Studies have found that when temporal lobe surgery
is within the language dominant hemisphere, additional memory impairment is often incurred (Lee, Yip, & Jones-Gotman, 2002; Wieser, 2004). Chelune et al. (1993) found that the LTL group had a 9% decrease on their WMS-R Verbal Memory Index score; the RTL group had a 2% increase. Decreased performance in verbal memory is more likely if baseline memory performance is higher (Meador, 2002). The Intracarotid amobarbital test (IAT), which was originally introduced to lateralize language, was modified in an attempt to predict the risk for post-operative amnesia. With the advent of modern imaging techniques (i.e., fMRI) and the IAT, risks of severe deficits following surgery may be minimized.

Assessment of language. Language disturbance or aphasia are not usually clinically obvious in TLE patients, but they frequently report experiencing word-finding difficulties (Oxbury, 2001). It is therefore preferable to select specific language tests rather than administer comprehensive aphasia batteries. Test of both receptive and expressive language functions should be included, as language comprehension and production involve different brain regions. Two preferred tests of language comprehension include The Token Test, and the Sentence Comprehension Test (Complex Ideational Material) from the Boston Diagnostic Aphasia Examination (BDAE) (Jones-Gotman et al., 1993). The Token Test provides commands of increasing complexity and was designed to assess language comprehension among aphasia patients (De Renzi & Vignolo, 1962; Spreen & Strauss, 1998). For example, a simple command may be “Touch the red circle.” A more complex command may be, “Put the small green circle under the large red square.” The Sentence Comprehension Test of the BDAE requires “yes” or “no” responses to questions, such as, “Will water go through a good pair of
rubber boots?”, and also to questions following four different paragraphs, indicating that a patient has comprehended each one. Tests of expressive language include The Sentence Repetition Test of the Multilingual Aphasia Examination (MAE), the Wide Range Achievement Test (WRAT), and the Boston Naming Test (BNT). The Sentence Repetition Test is commonly included in epilepsy batteries as a measure of language function; however, it is also considered a test of immediate memory (Spreen & Strauss, 1998). The WRAT Reading Test is designed to measure word recognition and pronunciation. The Boston Naming Test (BNT), a test of confrontation naming, is one of the most frequently used language tests for epilepsy patients (Jones-Gotman et al., 1993).

Language tests provide information about the hemisphere in which dysfunction occurs. Poor performance on such tests is interpreted as showing diminished function in the dominant hemisphere, while severe deficits alert us that damage is widespread in that hemisphere and extends beyond focal anterior temporal lobe dysfunction. To interpret an individual patient’s pattern, the result from language tests are contrasted to results on memory tests and visuospatial and perceptual tasks.

**Language lateralization.** There have been numerous suggestions that word-finding difficulty occurs in patients with left temporal lobe epilepsy (LTLE), most frequently on visual naming tasks, such as the BNT. In a comparison of groups of patients with left TLE, right TLE, and generalized epilepsy, Mayeux, Brandt, Rosen, and Benson (1980) found that groups differed only on the BNT, where patients with LTLE scored lower than the other groups. Oyegbile, Dow, and colleagues (2004) compared patients with temporal lobe epilepsy to healthy controls on 20 test measures. Patients exhibited worse performance across measures of intelligence, language, memory,
executive function, and motor speed (Oyegbile, Dow et al., 2004). While both left and right temporal lobe groups performed worse than controls, after controlling for age, gender and education, only the BNT approached significance in discriminating left and right patient groups (Oyegbile, Dow et al., 2004).

Findings have been inconsistent in studies of language function in patients with left TLE and right TLE prior to surgery (Oxbury, 2001). In general, LTLE patients performed worse on MAE language tests than RTLE patients (Hermann & Wyler, 1988; Hermann, Wyler, & Somes, 1991). Studies comparing left and right temporal lobe epilepsy patients have consistently found that LTLE patients were significantly more impaired on visual naming tests, such as the Boston Naming Test (Davies et al, 1994; Hermann, Seidenberg, Haltiner, & Wyler, 1992; Sass et al., 1992; Saykin et al., 1995).

Although patients with LTLE appear to be mainly impaired on visual naming tests, there are also indications that LTLE patients may be mildly impaired in other areas of language function (Oxbury, 2001). In addition, several studies have found some degree of deficit in RTLE patients (Ellis, Hillam, Cardno, & Kay, 1991; Langfitt & Rausch, 1996).

MTLE is generally associated with hippocampal dysfunction and memory impairment. Hermann et al. (1997) examined the relationship of language function to hippocampal sclerosis in patients with MTLE. They compared patients with hippocampal sclerosis (MTLE+) to patients with MTLE without hippocampal sclerosis (MTLE-) and found the group with left-sided MTLE+ performance significantly worse than the group with left-side MTLE- on naming (-5.2, 11%), aural comprehension (-1.7, 10%), and reading comprehension (-1.3, 7%) subtests. This suggests hippocampal involvement in both receptive and expressive language functions. They also found that
the group with right-sided MTLE+ performed significantly worse than the group with right-sided MTLE- on the name (7, 14%) and oral fluency (3, 9%) subtests. Patients with MTLE+, regardless of laterality, scored significantly lower than the MTLE- patients. Perrine et al. (1991) suggest that subtests related to verbal word production, confrontation naming, and aural/reading comprehension are the most predictive of memory impairment. They found that anomia can occur in patients with dominant hemisphere temporal lobe seizures, and if present, correlates strongly with verbal memory deficits.

1.5.3 Memory findings in temporal lobe epilepsy.

Hermann et al. (1997) noted that although temporal lobe epilepsy is typically associated with a number of generalized cognitive impairments, memory deficits are most prominent.

Among the most frequently used memory tests are measures from the Wechsler Memory Scales (Jones-Gotman, 1991). The scale has two major subdivisions, Verbal Memory and Visual Memory. Verbal memory subtests of the WMS include Logical Memory I&II (immediate and delayed), a measure of story recall, and Paired Associates I&II (immediate and delayed), which measure recall of word-pairs. Patients with a left temporal lobe lesion show significant impairment on these verbal subtests; patients with a right temporal lobe lesion show less impairment (Jones-Gotman, 1991). Although patients with left temporal lobe focus typically perform worse on story recall than right temporal patients, some right temporal focus patients also recall stories poorly. Visual Reproduction, Immediate and Delayed, are commonly used as the non-verbal memory measures of the WMS. On the Visual Reproduction subtests, the four geometric designs to be recalled can be easily verbalized. Despite this clearly verbal factor, this test can
elicit a material specific impairment from patients with right temporal lobe damage (Jones-Gotman, 1991). In a study of presurgical patients, Moore and Baker (1996) were able to lateralize left hemisphere impairment, but found the assessment of right hemispheric impairment more problematic. They found that the Verbal/Visual Memory discrepancy scores incorrectly identified most patients with right temporal focus, resulting in questionable validity of this Index (Moore & Baker, 1996). Jones-Gotman et al. (1993) suggested that the difficulty in lateralizing left and right hemisphere impairment might be due in part to the fact that the three principal parts of the WMS (Logical Memory, Paired Associates, & Visual Reproduction) are predominantly verbal and thus biased to detect dominant temporal lobe dysfunction. Although these material-specific learning deficits can be observed in patients with unilateral temporal lobe seizure onset, the magnitude of the verbal/visuospatial memory asymmetry is greater following temporal lobectomy (Novelly et al., 1984). The most recent revision of the WMS (the WMS-III) includes a visual memory subtest (Faces I and II) that measures the ability to recognize faces immediately following presentation and again after a 30-minute delay. Although the Faces subtest has been a popular addition to a standard memory battery in temporal lobe epilepsy, Wilde et al. (2001) found it to lack the ability to differentiate laterality of disturbance in patients with temporal lobe epilepsy. On the other hand, Doss, Chelune and Naugle (2004) found it was able to significantly discriminate right temporal lobectomy and left temporal lobectomy patients. As the significance of the Faces subtests has yet to be determined, it has been suggested that caution be exercised in interpreting contrasts between verbal and visual indexes of the WMS-III (Wilde et al., 2003). In differentiating between immediate and delayed recall modalities of the WMS
subtests, Jones-Gotman (1991) found delayed recall to be more sensitive to dysfunction than immediate recall. A factor analytic study of WMS-R found a significant delayed recall factor with loadings from both verbal and non-verbal tasks (Perrine et al., 1991). Conversely, neither Bell, Hermann and Seidenberg (2004), nor Wilde et al. (2003) found significant differences between immediate and delayed memory measures.

The Memory Assessment Scales (MAS) (Williams, 1991) is an alternative to the WMS-R, and it consists of 12 measures of learning, recent memory and attention/concentration. Performance scores on these measures generate summary indices of General Memory, Verbal Memory, Visual Memory and Short-Term Memory. The MAS has been found to be sensitive to material-specific memory deficits associated with unilateral temporal lobe seizure onset (Loring, Hermann, Lee, Drane & Meador, 2000). Loring et al. (2000) found a significant multivariate group difference for Verbal, Visual and General Memory indices ($F=2.89, p<0.04$). Although univariate group differences were not found to be statistically significant for General Memory and Verbal Memory indices, a significant difference was found Visual Memory ($t_{(99)}=2.06, p<0.04$). In addition, in testing for Verbal Memory-Visual Memory discrepancy, a statistically significant group effect was found between the indices ($t_{(99)}=2.93, p<0.004$), indicating the test’s ability to correctly lateralize temporal lobe dysfunction. Comparisons of the WMS-R and the MAS have resulted in inconsistent findings (Golden, White, Combs, Morgan & McLane, 1999; Hilsabeck, Dunn, & Lees-Haley, 1996; Lazarus, Small & Williams, 1996; Putnam et al., 1994; Zielinski, 1993). Hilsabeck et al. (1996) found that traumatic brain injured patients scored significantly lower on the MAS than on the WMS-R. Lazarus et al. (1994), using a sample of patients with mild brain injury of varying
etologies, and Putnam et al. (1994), comparing patients with mild head injury, reported statistically significant, but moderate correlations among the verbal, visual and global indices. Golden et al. (1999) noted some interesting correlations among indices. The WMS-R Verbal Index revealed a stronger correlation with the MAS Verbal than the MAS Visual Index; however, the WMS-R Visual Index showed strong Verbal and Visual correlations with the MAS (Golden et al., 1999). This underscores the role of verbal skills in the WMS-R Visual Index.

In a test-by-test comparison, Zielinski (1993) found that differences in subtests are the result of actual differences in what they measure. For example, he suggested that the difference between the Logical Memory subtest of the WMS-R and the Prose Memory subtest of the MAS was that Logical Memory measures retrieval processing; whereas, Prose Memory measures consolidation (Zielinski, 1993). There are clear differences between the two tests, probably intentional, as the purpose of developing the MAS was to improve upon the original WMS due to widespread dissatisfied in its design. Golden et al. (1999) suggested that the subtests measured what they purported to measure, but the indices were inefficient. The authors proposed that rather than there being a General Memory Index or Verbal Memory Index, there may be strengths and weaknesses of very specific types of memory. They also suggested that it might be beneficial to include parts of both batteries with other tests in order to get a good picture of a wide sample of memory functions (Golden et al., 1999).

**Other tests of memory - verbal measures.** List learning tests are commonly used as additional measures of verbal learning and memory. Although WMS measures are widely used to assess memory function, the Paired Associates test is not considered the
best listing learning measure, as only 4 of the 10 word-pairs even tax memory (Jones-Gotman et al., 1993). The California Verbal Learning Test (CVLT) is a more suitable list-learning paradigm that is popularly used. The CVLT assesses episodic verbal memory and has been found to be sensitive to hippocampal function (Martin et al., 2002). The CVLT is a very useful test, as it can examine not only immediate and delayed recall and recognition, but other aspects of memory as well, such as learning over several trials, serial position effects, and the effects of interference on recall. In the CVLT, indices of learning rates across trials are provided, as well as perseverations and intrusions in recall, recall consistency across trials, and semantic and serial learning strategies (Spreen & Strauss, 1998). Three measures of the CVLT assess specific aspects of verbal memory: Acquisition (measured by total word recall across trials 1-5), Retrieval (measured by total words recalled following a 20 minute delay), and Recognition (measured by calculating the ratio of true hits to false-positive errors) (Martin et al., 2002).

Non-verbal measures of memory. Non-verbal memory tests include the Rey Osterrieth Complex Figure Test, a test of memory for designs. This measure, along with the Visual Reproduction subtest from the WMS, can be easily verbalized, thereby reducing the power to discriminate left from right temporal lobe dysfunction. Repeated exposure to material to be remembered can help differentiate impaired and unimpaired individuals, as unimpaired individuals benefit more from the additional exposure (Jones-Gotman et al., 1993).

Jones-Gotman (1991) noted that not all memory measures are sensitive to damage in the hippocampus, including the WMS, and suggests that the temporal neocortex may be as important as the hippocampus for efficient performance on WMS tests. On the
other hand, efficient performance on some tasks does appear to depend on the integrity of hippocampal structures, such as memory for abstract designs and list learning tasks (i.e., CVLT). Research has shown that individuals with relatively severe hippocampal pathology may perform within the average range on List A, Trial 1, but experience difficulty incorporating new information that is beyond their basic attention span (Banos et al., 2004). The index of Percent Retention from the WMS was also found to correlate with hippocampal neuron loss (Martin et al., 2002).

**Mesial temporal lobe epilepsy.** In mesial temporal lobe epilepsy, hippocampal sclerosis (HS) is a defining characteristic (Hermann et al., 1997; Wieser et al., 2001). Hippocampal sclerosis is associated with material-specific memory deficits, and is not typically associated with generalized and diffuse neuropsychological impairment (Hermann et al., 1997). A study of patients comparing MTLE with hippocampal sclerosis to patients with MTLE without, or with mild sclerosis, found that patients with MTLE with hippocampal sclerosis demonstrated considerable generalized cognitive impairment, in intelligence, academic achievement, language, and visuospatial functions (Hermann et al., 1997).

The hippocampus is especially involved in learning, and patients with hippocampal damage also forget sooner than patients with no hippocampal damage or with damage to neocortical regions (Jones-Gotman, 1991). Cognitive impairment in MTLE usually involves “episodic memory” (i.e., impairment of the long-term memory consolidation or retrieval of newly acquired information), whereas, impairment of semantic memory is less likely (Wieser, 2004). Depending on the hemisphere of language dominance and the affected hemisphere, material-specific memory impairment
is found in TLE. Verbal long-term memory is usually much more affected than is figural memory. However, Gleibner, Helmstaedter and Elger (1998) compared pre-surgical patients with RTLE with and without hippocampal sclerosis and found that the group with HS demonstrated impaired visual memory performance, whereas, the non-sclerotic group did not exhibit any impairment of the assessed functions. Wieser (2004) found that the degree of memory impairment in MTLE is associated with several factors: the degree of hippocampal sclerosis, the extent of neuronal loss, and the degree of bilaterality. These factors have been examined in other studies with varying results. Kilpatrick et al. (1997) also found an association between the degree of hippocampal sclerosis and memory impairment, but only in terms of the left hippocampus. They examined both verbal and non-verbal memory and found that the degree of left hippocampal atrophy in patients with left temporal lobe epilepsy was associated with severity of verbal memory deficits. No association was found between the degree of right hippocampal atrophy and any of the memory tests. An association was also found between the degree of left hippocampal atrophy and measures of non-verbal function.

Neuronal loss, as assessed by cell counts in different hippocampal subfields, is another factor associated with the degree of memory impairment. This finding is consistent with other research (Bell, Davies, Haltiner, & Walters, 2000; Martin et al., 2002). Hermann et al. (1994) reported a direct relationship between the amounts of cell loss in resected hippocampi and preoperative performance on memory tests. A factor analysis on the principal components of the CVLT found that on the General Memory Factor, left hemisphere lobectomy patients without significant hippocampal sclerosis tended to perform better than those with sclerosis at preoperative assessment,
significantly so for measures of short- and long-delay free recall (Hermann et al., 1994). This pattern was completely reversed at the time of postoperative testing for all indices. Left-ATL patients without hippocampal sclerosis performed significantly worse postoperatively than the hippocampal sclerosis group on several other CVLT indices. Minimal pre- to postoperative change was exhibited by the moderate/severe hippocampal sclerosis group. Sass et al. (1994) found that postoperative patients with mild or moderate left hippocampal neuron loss experienced significant verbal memory decline, but the memory of postoperative patients with severe left hippocampal neuron loss did not decline significantly. Sass and colleagues (1994) noted that the neuronal cell loss was specific to verbal memory impairment. Patients undergoing right ATL exhibited significant improvements in verbal memory, regardless of the condition of excised hippocampal tissue (Sass et al., 1994).

Finally, the extent of bilaterality, found by MRI volumetry/spectroscopy, correlates with the degree of memory impairment (Wieser, 2004). This finding was supported by a study conducted by Jones-Gotman (1991) in which four temporal lobe epilepsy patient groups were compared on WMS verbal measures. Two groups had clear unilateral seizure focus with epileptic abnormalities confined to one side, and two other groups had bi-temporal abnormalities but with a predominant focus (bi-temporal with predominantly left focus and bi-temporal with predominantly right focus). Patients with an abnormality of primarily the left temporal lobe, but with additional damage on the right were the most profoundly impaired (Jones-Gotman, 1991). This study demonstrated that bi-temporal patients performed significantly worse than unilateral focus groups, but showed the expected patterns for their lesion group. As previously
noted, other research has found that the degree of left hippocampal atrophy was associated with poor performance on measures of non-verbal memory, suggesting that the left hippocampus may be implicated in non-verbal memory or that MTS is a bilateral but asymmetrical condition (Kilpatrick et al., 1997). The famous study of HM (Scoville & Milner, 1957) in which both hippocampi were resected resulting in complete anterograde amnesia, is further testament to the notion that bilateral damage to hippocampi increases the degree of memory impairment. Additional determinants of memory impairment in MTLE are the variables purported to impact cognition in general in patients with epilepsy (i.e., age at onset, medication, frequency of seizures, cognitive reserve, etc.). Temporal lobe surgery, particularly within the language dominant hemisphere, has been associated with additional memory impairment (Jones-Gotman, 1991; Wieser, 2004). Often additional memory loss is incurred, with verbal memory being most often affected (Lee, et al., 2002). In patients undergoing hippocampal resections, the extent of tissue removal impacts the amount of memory impairment, especially in the language dominant hemisphere (Wieser, 2004). Clusmann et al. (2002) noted that fewer memory difficulties are found with more selective surgery than the standard two-thirds surgery. Conversely, Graydon, et al. (2001) found that the extent of unilateral temporal lobectomy played a relatively small part on memory function outcome.

**Lateralization of memory functions.** Generally speaking, in post-surgical patients with unilateral temporal lobe seizure focus, material-specific deficits are observed. Memory deficits for verbal material are seen after dominant temporal lobe injury and visuospatial memory deficits are seen after injury to the non-dominant temporal lobe (Jones-Gotman, 1991). Verbal memory deficits lateralize to the left
hemisphere if the left hemisphere is the “language-dominant” hemisphere. Delaney, Rosen, Mattson, and Novel (1980) reported that non-verbal visual memory deficits were found in right temporal seizure patients compared with control groups, and this was especially true for delayed recall. Laterality of focus is more likely to be achieved when differences are seen between verbal and visuospatial task performance of material-specific learning on a consistent basis over several measures. When atypical material-specific test results are found, it is important to consider whether the patient’s handedness or language lateralization could account for these findings (Baker & Goldstein, 2004).

Presurgically, material specific effects may be present, but are more prominent for verbal material with left foci than for non-verbal memory impairment with right foci (Perrine et al., 1991). Patients with a right temporal lobe lesion show a memory deficit specifically for material that cannot be verbalized easily (e.g., faces, abstract designs, melodies, and spatial locations) (Jones-Gotman, 1991). Both left and right temporal lobe seizure patients show relative deficits in the recall of narrative material on immediate and delay trials on verbal but not non-verbal memory tasks (Perrine et al., 1991). Failure to differentiate lateralized TLE may be due the fact that the association between verbal memory and the left temporal region is more robust than that between visual memory impairment and right temporal dysfunction, with too many false positives in the left temporal group (Perrine et al., 1991; Wieser, 2004). One possible explanation for the weak associations of non-verbal material and right temporal lobe patients is that different memory tests for verbal or non-verbal episodic memory might not be equally sensitive to the lateralization of TLE and mesial pathology (HS) (Wieser, 2004). Possible explanations for the weak effect may be compensation of visual memory impairment by
verbalization techniques, atypical language dominance, and possibly even gender differences (Wieser, 2004).

**Memory mechanisms.** Studies have revealed the importance of the hippocampal formation and the amygdala for learning and memory. Encoding of new information has been associated with the hippocampal formation, in particular with the perirhinal and entorhinal cortices (Wieser et al., 2001). More specifically, Schwarcz and Witter (2002) have identified the entorhinal cortex as the key structure associated with medial temporal lobe epilepsy, as it orchestrates the information flow to and from the hippocampus and plays an important role in cognitive dysfunction. The presence of spike-wave discharges in the left hippocampus have been found to disrupt the processing of learning and memory, and direct stimulation of the hippocampal structures can interfere in the consolidation of memories (Perrine et al., 1991). This leads to deficits in delayed recall and the presence of verbal intrusion errors. It has been found that patients with left temporal lobe foci commonly exhibit memory impairment, although significant memory dysfunction can occur in patients with right temporal lobe foci (Perrine et al., 1991).

It seems likely that the neuropathological substrate of the intractable seizures is more predictive of neuropsychological status than is laterality of a lesion (Hermann et al., 1997; Saykin et al., 1995; Strauss, Hunter, & Wada, 1995).

**Post-surgical findings.** The risk of declines in verbal learning and recall ability following left temporal lobe surgery has been established (Chelune, Naugle, Luders & Awad, 1991; Dodrill et al., 1993; Graydon et al., 2001; Hermann, Wyler, Somes, Berry, & Dohan, 1992; Jones-Gotman et al., 1997; Martin et al., 2002; Novelty et al., 1984; Sass et al., 1994). The greatest risk of memory loss has been found in patients who have the
most intact preoperative memory function (Dodrill et al., 1993). This is possibly due to the extent of hippocampal sclerosis, and therefore the functional capacity, of the resected hippocampus. Postoperative declines in nonverbal, visual-spatial, abilities following surgery on the right are inconsistent (Dodrill et al., 1993).

Verbal declarative memory requires the collaborative effort of at least two functionally distinct brain systems: working memory is mediated by neocortical temporal structures; while long-term consolidation/retrieval is mediated by mesial temporal structures (Helmstaedter, Grunwald, Lehnertz, Giebner and Elger, 1997).

Unlike the left temporal neocortex, the function of the mesial temporal structures appears to be material non-specific; its involvement in verbal memory is likely due to its close proximity to neocortical structures that are specialized for language processing (Helmstaedter et al., 1997).

**Lateral neocortical versus mesial temporal lobe epilepsy.** Evidence suggests that there are multiple memory systems involving declarative and non-declarative memory governed by distributed neural networks. If the hippocampi and related cortical structures are damaged or destroyed, severe impairment of declarative memory can occur. Conversely, non-declarative procedural or skill-related learning, conditioning, and priming remain preserved (Helmstaedter et al., 1997).

The mesial temporal lobe system mediates long-term declarative memory and is preferentially involved in fast and time-limited consolidation processes of memory contents. Neocortical structures are assumed to mediate short-term or working memory and to house a storage area for information (Helmstaedter et al., 1997).
The majority of patients who will be treated surgically to alleviate epileptic seizures have a temporal lobe focus. In these cases, the question of whether the hippocampus is functioning adequately is particularly important. Because the extent of hippocampal excision can vary, it is possible to study the contribution of the anterior hippocampus to memory. Different patterns of results emerge as a function of different types of memory measures. Some memory functions rely more heavily on the hippocampus than others, which depend on the temporal neocortex. Investigations of global amnesia in humans have shown that bilateral destruction of the hippocampi and related cortical structures can lead to severe impairment of declarative memory performance; however, non-declarative procedural or skill-related learning, conditioning, and priming remain preserved to a large extent.

Seizures originating in the lateral neocortical temporal lobe cortex are far less common than seizures originating in the mesial temporal lobe structures (Wieser et al., 2001). It is not unusual, however, for neocortical regions to be affected by seizures originating from mesial temporal lobe regions (Adam, Saint-Hilaire, & Richer, 1994; Lieb, Dasheiff, & Engel, 1991; Weiser et al., 2001).

1.6 Extratemporal Deficits

The neuropsychological deficits associated with the temporal lobe, and more specifically, the hippocampus, are well established in MTLE. They do not, however, explain all of the deficits associated with this syndrome. It is expected that memory and language deficits occur due to the disruptive effects of seizure activity in the temporal lobes and their reliance on the proper functioning of that region. What is less obvious are the additional deficits noted outside of these domains in patients with MTLE. There is a
growing body of evidence that brain abnormalities in MTLE, even in well-defined cases of unilateral MTLE, occur outside of the epileptogenic region, extending into widespread areas of extrahippocampal temporal and extra-temporal regions (Kim et al., 2003).

Several studies have documented that cognitive dysfunction in TLE can extend to other domains, including executive functions, that are not ordinarily considered to be affected by temporal lobe pathology (Corcoran & Upton, 1993; Hermann & Seidenberg, 1995; Hermann et al., 1996; Hermann, Wyler & Richey, 1988; Martin et al., 2000; Shulman, 2000; Strauss, Hunter & Wada, 1993; Trenerry & Jack, 1994).

1.6.1 Neuroimaging studies.

Electroencephalography (EEG). Recent investigations using functional imaging suggest that frontal lobe dysfunction appears to play a crucial role, even among patients with temporal lobe seizure foci (Shulman, 2000). Neuroimaging studies have been able to clearly identify abnormalities outside of the epileptogenic region in a variety of ways. Invasive EEG procedures have demonstrated seizure activity spread often emanating from the mesial temporal lobe to the ipsilateral frontal lobe (Shulman, 2000). Electroencephalographic (EEG) recordings have often shown widespread propagation of epileptic activity towards other brain areas ipsilaterally and contralaterally (Exner et al., 2002). Blumenfeld et al. (2004) found prominent irregular slow-wave activity in regions outside of the temporal lobe during temporal lobe seizures. Areas most dramatically affected were the bilateral frontal and the ipsilateral parietal association cortex (Blumenfeld et al., 2004). In a study by Lieb et al. (1991) using depth EEG electrodes in patients with unilateral mesial temporal lobe epilepsy, both bilateral frontal and
contralateral mesial temporal lobe seizure activity were noted demonstrating distinctive patterns of ictal spread.

**Single photon emission computed tomography (SPECT).** Neuroimaging studies using SPECT have also revealed regions of physiological abnormality beyond the epileptogenic temporal lobe (Shulman, 2000). Increased cerebral blood flow (CBF) is associated with epileptic activity in the temporal lobe on the side of seizure onset. Van Paesschen (2004) noted that there are typical perfusion patterns in mesial temporal lobe epilepsy with hippocampal sclerosis. These patterns demonstrate ipsilateral temporal lobe and frontoparietal hypoperfusion, and contralateral cerebellar hypoperfusion. In a study using SPECT, Blumenfeld et al. (2004) also found decreased CBF in the frontal and parietal cortex during temporal lobe seizures. These CBF changes indicate that even when seizure activity are confined to temporal lobe structures, more widespread impairment of function may occur in extratemporal structures such as the frontal and parietal neocortex (Blumenfeld et al., 2004).

**Positron Emission Tomography (PET).** Positron Emission Tomography (PET) investigations of patients with MTLE have shown that areas of hypometabolism extend beyond the epileptogenic temporal lobe. Henry, Mazziotta, and Engel (1993) found regional hypometabolism in 25 of 27 TLE patients in extratemporal regions including the ipsilateral thalamus (63%), basal ganglia (41%), frontal (30%), parietal (26%), and occipital (4%) regions (Hermann & Seidenberg, 1995). In a study comparing patients with MTLE to healthy controls, Arnold et al. (1996) reported depressions of regional cerebral glucose metabolism (rCMRGlu) ipsilateral to the epileptic zone in the mesiotemporal region that included the hippocampus, the parahippocampal gyrus, and
middle temporal gyrus. In addition, remote depressions were found bilaterally in the fronto-orbital cortex and ipsilaterally in the posterior insula and thalamus (Arnold et al., 1996). In patients with left sided MTLE rCMRGlu depression was noted in the left inferior frontal gyrus (Broca’s area) and the superior temporal gyrus at the parietotemporal junction, whereas corresponding rCMRGlu depressions were not present in patients with right MTLE.

During investigations involving several functional imaging modalities, as well as structural MRI, Wieser (2004) noted consistent abnormalities distributed beyond the affected hippocampus in MTLE with hippocampal sclerosis. These abnormalities primarily affect the contralateral hippocampus and the ipsilateral limbic system areas of the frontal and temporal lobes; however, limited ipsilateral neocortical involvement is also frequently present. Magnetic resonance spectroscopy (MRS), and in particular proton magnetic resonance spectroscopy ($^1$H MRS), indicates neuronal loss and gliosis by measuring reduced N-acetylasparte/choline ratios. MRS imaging is a useful tool for indicating neurometabolic compromise and has proven extremely useful in detecting cell abnormalities outside of the epileptogenic zone (Cendes, Andermann, Dubeau, Matthews & Arnold, 1997; Tasch et al., 1999; Vermathen et al., 1997).

### 1.6.2 Neuropsychological examinations.

Neuropsychological evaluation provides an additional method of detecting and localizing impairment of cognitive functions. Cognitive dysfunction in TLE can extend to other domains, including executive functions, that are not usually believed to be affected by temporal lobe pathology (Martin et al., 2000). Many temporal lobe epilepsy patients have been found to perform worse than healthy control subjects on a variety of
neuropsychological tests, including executive control and intelligence measures (Helmstaedter et al., 1996; Hermann, Wyler, & Richey, 1987; Upton & Thompson, 1996). Upton & Thompson (1996) suggested that performance on executive functions may be impaired among temporal lobe epilepsy patients due to interictal spread.

Epileptogenic tissue is not only malfunctions, but also adversely influences remote cerebral structures resulting in additional cognitive deficits (Engel, Bandler, Griffith, & Caldecott-Hazard, 1991; Luders & Awad, 1991). One measure often used to detect frontal damage is the Wisconsin Card Sort Test (WCST). Performance on the WCST, particularly the measures of perseverative responding, is especially sensitive to frontal-lobe function, most notably, the dorsolateral prefrontal cortex (DLPFC) (Hermann et al., 1988). The WCST index that most clearly discriminates frontal lobe patients from epilepsy controls is the number of perseverative errors (Milner, 1963). Several studies have found that patients with temporal lobe epilepsy perform poorly on the WCST (Corcoran & Upton, 1993; Hermann & Seidenberg, 1995; Hermann et al., 1988; Strauss et al., 1993). Hermann et al. (1988) found that a large proportion of patients with temporal lobe epilepsy perform on the WCST in a manner suggestive of frontal lobe dysfunction. A total of 57% (74% of non-dominant and 39% of dominant) of temporal lobe patients obtained 20 or more perseverative responses on the WCST, a performance that is suggestive of frontal lobe impairment (Hermann et al., 1988). In an investigation comparing the performance of TLE and FLE patients on the WCST, Exner et al. (2002) observed an overlap of impaired functions, with temporal lobe epilepsy patients demonstrating impairment representative of frontal lobe dysfunction (i.e., a high number
of perseverative errors on the WCST), and frontal lobe epilepsy patients showing impairment typical of temporal lobe dysfunction (i.e., memory deficits).

Efforts to determine the hemisphere most affected by performance on the WCST have resulted in conflicting findings. Several studies reported that more perseverative responding and poor WCST performance occurs in patients with right hemisphere damage rather than left (Corcoran & Upton, 1993, 1995; Heaton, 1981; Hermann et al., 1988; Robinson, Heaton, Lehman, & Stilson, 1980). Conversely, other studies have found that more perseverative responding was associated with left hemisphere dysfunction (Giovagnoli, 2001), or bilateral dysfunction (Berman et al., 1995; Nagahama et al., 1996). Strauss et al. (1993) found that left temporal lobe dysfunction causes more perseverative responses, but only if onset of seizures was before one year of age. Right TL dysfunction also causes perseverative responses, but to a lesser degree (Strauss et al., 1993). Trennery and Jack (1994) were not able to detect WCST differences between right and left lobectomy patients before or after surgery. Martin et al. (2000) found that executive abilities, as measured by the WCST, Trails B test, and verbal fluency, were not sensitive to lateralization of TLE, but that 27% to 50% of patients with TLE displayed at least a mild level of impairment on such measures.

Verbal fluency has also been associated with frontal lobe function, particularly in the language-dominant hemisphere (Oxbury, 2001). Martin, Loring, Meador, and Gregory (1990) found that patients with LTLE performed worse than those with RTLE on both letter and semantic fluency tasks, and RTLE patients were impaired compared to normal controls. Corcoran and Upton (1993) found that TLE patients with lateral TL pathology showed the same degree of impairment as those with FLE, while TLE patients
with HS performed better, suggesting that both temporal and frontal regions participate in systems necessary for word fluency performance (Oxbury, 2001).

Hermann, Wyler, and Somes (1991) suggested that executive impairment in TLE patients could result from either the direct spread of temporal lobe hypometabolism to the frontal lobe or the effect of temporal lobe hypometabolism spread to the thalamus secondarily affecting the frontal lobe. In studies examining the post-surgical effects of extra temporal deficits, it was found that these remote deficits normalized, or returned to normal, upon cessation of seizure activity.

**Nociferous cortex hypothesis.** The nociferous cortex hypothesis states that “epileptogenic cortex adversely affects the extratemporal regions that mediate executive system abilities, thereby resulting in performance deficits” (Hermann & Seidenberg, 1995, p. 809). These effects are caused by the propagation of abnormal discharges from the epileptogenic (nociferous) cortex to healthy brain regions. The theory also predicts that normalization of extratemporal functions will take place following surgical resection of damaged tissue, which will result in improvements in executive functioning (Martin et al., 2000).

The premise of the nociferous cortex hypothesis is that impairment in executive functioning in patients with temporal lobe epilepsy is caused by the noxious effects of the epileptogenic tissue, but not by the structures themselves. This is supported by the fact that performance does not decline following resection of epileptogenic lesions, but rather, often results in improvement of ipsilateral and contralateral cognitive functions. It is clear that the executive system deficits that occur in TLE are not directly attributable to temporal lobe/hippocampal compromise, but rather due to the influence of nociferous
cortex on extratemporal systems. The basis of this theory becomes apparent with an understanding of the neural mechanisms and propagation patterns that underlie the structure of this system.

1.6.3 **Neural mechanisms and propagation patterns.**

*Neural mechanisms.* Propagation of ictal discharges to remote brain regions is accomplished through a number of neural pathways that connect one region of the brain to another. There is an abundance of association fibers within each hemisphere, as well as commissural fibers between hemispheres that are available as pathways for propagation (Emerson, Turner, Pedley, Walczak, & Forgione, 1995). Studies have demonstrated preferential seizure spread from epileptogenic mesial temporal lobes to the mesial frontal lobes, and there is strong evidence that the frontal lobes are closely connected with mesial temporal lobe structures (Lieb et al., 1991). Information reaches prefrontal structures through connections with association cortex of all sensory modalities, and with posterior association cortices (Shulman, 2000). One way that mesial temporal lobe structures, such as the hippocampus, and anterior temporal areas connect to the frontal lobes, especially the orbitofrontal cortex, is via the uncinate fasciculus. The inferior longitudinal fasciculus connects points along the superior, middle, and inferior temporal gyri with occipital cortex and might support propagation between anterior and posterior lateral temporal neocortex (Emerson et al., 1995). Upton & Thompson (1996) found that cortical connections between the temporal and frontal regions are numerous, and through these connections it is likely that epileptic discharges in one area may cause deficits in another area. Schwarcz & Witter (2002) suggest that within the hippocampus, the entorhinal cortex acts as a type of relay station that regulates the flow of information
to and from the hippocampus and plays a major role in cognitive dysfunction. The prefrontal lobes also have connections with three limbic systems: the corticolimbic regions; subcortical limbic regions, and visceral-endocrine peripheral nervous system.

The prefrontal cortex is the only area in the nervous system that receives and integrates information from both the somatosensory and the limbic-sensory systems (Shulman, 2000). The manner in which interhemispheric propagation is conducted is poorly understood; however, the hippocampal commissure may be implicated in interhemispheric propagation (Adam et al., 1994). Lieb et al. (1991) have suggested that subcortical pathways may be the primary route taken by mesial temporal seizures for interhemispheric propagation and may mediate temporal to frontal spike propagation (Emerson et al., 1995; Hermann et al., 1988). Although many possible propagation pathways have been elucidated, there are still many unnamed association fibers that may support spike propagation (Emerson et al., 1995).

Seizure propagation. Seizure propagation patterns are not random, but follow preferred pathways that correspond to the neuroanatomical connections between brain regions (Wieser, 2004). Invasive EEG procedures have demonstrated preferential seizure spread from the mesial temporal lobe to the ipsilateral frontal region, and preferential propagation of interictal spikes from mesial temporal to mesial and orbitofrontal regions (Shulman, 2000). The mode of transhemispheric propagation is not well understood, but it might be transcallosal once the ipsilateral frontal lobe is activated by a seizure (Wieser, 2004).

Propagation patterns. An investigation of trends in propagation patterns resulted in the following observations: (a) the ipsilateral frontal lobe (IFL) has been found to be
the most frequent first site of propagation; (b) the second most commonly invaded is the contralateral temporal lobe (CTL) and lastly, the contralateral frontal lobe (CFL); (c) in terms of their position in the propagation sequence, the IFL is invaded before the CFL more often than the opposite, and the CTL is involved before CFL more often than the opposite, but the CTL is invaded before the IFL in many seizures; (d) the mesial structures are invaded earlier than lateral structures (Adam et al., 1994).

Lieb et al. (1991) described a common pattern of seizure spread during complex partial seizures: from the initiating temporal lobe to the ipsilateral frontal lobe, especially the orbitofrontal cortex, to contralateral frontal lobe and then to contralateral temporal lobe (Emerson et al., 1995). The same propagation pattern was observed by Paradiso et al. (1995) in their study of strychnine-induced epileptics. Adam et al. (1994) also observed that seizure propagation to frontal lobes was sequential, with the IFL invaded before the CFL. Lieb et al. (1991) suggested that the ipsilateral frontal lobe might be driving seizure activity in the contralateral frontal lobe.

While this pattern commonly occurs, propagation pathways are variable and can deviate from the pattern reported by Lieb et al. (1991) and others (IFL, CFL & CTL successively) (Adam et al., 1994). The contralateral temporal lobes can be invaded independently of the frontal lobes (Adam et al., 1994). Wieser (2004) noted that there is evidence that ipsilateral frontal or orbitofrontal ictal involvement is not a necessary condition for seizure spread to contralateral mesial TL. The CTL can be initially invaded mesially, without the commonly observed frontal or lateral CTL involvement (Adam et al., 1994; Spencer, Williamson & Spencer, 1987). A study by Lieb et al. (1991) found that CTL involvement might even precede or appear simultaneously with frontal lobe
invasion. It is therefore possible that ictal propagation can sometimes proceed through a more direct pathway than the frontal one, such as the hippocampal commissure (Adam et al., 1994).

When the epileptogenic zone is the hippocampus, propagation usually invades the ipsilateral temporal neocortical areas first, with variable subsequent involvement of frontal and contralateral structures (Wieser et al., 2001). However, about 30% of hippocampal onset seizures appear first in the contralateral hippocampus before invading the ipsilateral or contralateral temporal neocortex (Wieser et al., 2001).

Another possibility is that there are patients in whom seizure activity only invades the frontal lobes, without involvement of the contralateral temporal lobes (Lieb et al., 1994).

Occasionally, the CTL can be invaded prior to invading the CFL, but more often, seizure activity appeared in the IFL and CFL prior to appearing in the CTL (Lieb et al., 1994). Wieser (2004) noted that spread to the ipsilateral neocortical TL might occur as often as spread to the contralateral mesial TL structures without involvement of the ipsilateral neocortical TL. Interhemispheric propagation does not necessarily proceed in one direction, but can spread through multiple pathways; at least one to IFL and one to CTL (Adam et al., 1994).

In summary, there are a variety of neural pathways that are possible propagation routes in temporal lobe epilepsy. Propagation patterns can vary but most often begin at the epileptogenic temporal lobe and then invade the ipsilateral frontal lobe, the contralateral frontal lobe, and finally, the contralateral temporal lobe. The prefrontal region, especially the orbitofrontal cortex, is strongly influenced by mesial temporal
seizure activity, and may play a role in the interhemispheric propagation of mesial temporal seizures.

1.6.4 Possible explanations for extratemporal deficits.

Evidence of cognitive deficits that occur outside of the epileptogenic temporal lobe in temporal lobe epilepsy is prevalent, but to date there have been no adequate explanations for these effects. Jokeit et al. (1997) suggest that malfunctioning tissue in the epileptogenic zone adversely influences remote cerebral structures, resulting in additional cognitive deficits. This explanation, while accurate, provides little insight into the manner in which these distal deficits occur. There are several theories that may offer possible explanations for extratemporal deficits. These theories include: undiagnosed seizure activity, secondary epileptogenesis, diffuse metabolic pathophysiology, and diaschisis.

Undiagnosed seizure activity. Undiagnosed seizure activity in extratemporal regions is one way that extratemporal deficits may occur. Among patients with short, non-convulsive seizures, the effects of seizure activity may be missed (Aldenkamp & Arends, 2003). EEG monitoring is useful in identifying seizure activity that may not otherwise be apparent. Seizures are often infrequent events in many patients, and making EEG recordings of ictal activity could be both time-consuming and expensive (Huppertz et al., 2001). Seizure activity may also be missed when it emerges as subclinical epileptiform (interictal) discharges. Interictal discharges occur in the intervals between seizures. The ability to identify interictal activity has greatly advanced with modern imaging techniques. Continuous video EEG monitoring will aid in the detection of both ictal and interictal events.
Structural imaging methods, such as magnetic resonance imaging (MRI), are very helpful in locating structural damage, such as hippocampal atrophy that often follows prolonged seizure activity. While MR imaging is quite useful in detecting structural abnormalities, it cannot be used to detect seizure activity. In addition, MRI changes cannot be detected in many patients with TLE (Tasch et al., 1999). As a result, seizure activity may be overlooked. Magnetic Resonance Spectroscopic (MRS) imaging is a more sensitive indicator of neuronal dysfunction that uses a non-invasive method of detecting metabolic abnormalities. MRS imaging has proven highly effective in detecting abnormalities resulting from seizure activity that were previously missed by other assessment methods.

Surface EEG scans and 18-F FDG PET scans have also been found to be ineffective in localizing epileptogenic foci in neocortical temporal lobe epilepsy, especially when the focus is deep (Benbadis, 2001; Kim et al., 2003). The ability to detect epileptogenic activity is not infallible, but with the advent of modern imaging methods and cutting-edge technology, such as MRS imaging, the occurrence of undiagnosed seizure activity is less likely.

**Secondary epileptogenesis.** Another explanation for extratemporal deficits is secondary epileptogenesis. It has been proposed that a prolonged history of uncontrolled seizures could result in secondary epileptogenesis at sites distant to the lesion (Eliashiv, Dewar, Wainwright, Engel, & Fried, 1997). The earlier the onset of epilepsy, the more likely it is that seizure activity spreads and propagates to new areas. Morrell (1985) demonstrated that as the frequency of seizures increases, the likelihood of a secondary focus becoming permanent also increases. Secondary epileptogenesis occurs when a
region, separated from the primary epileptogenic area by at least one synapse, is impacted by seizure activity from that primary zone. The cortex in the secondary epileptogenic area is normal apart from the changes brought about by the primary epileptogenic area (Acharya, 2002).

Secondary epileptogenesis most likely occurs due to kindling, a phenomenon characterized by repeated, brief low frequency electrical stimulation of brain structures. This repeated electrical activity produces spontaneous epileptiform activity within weeks to months (Cibula & Gilmore, 1997). The epileptiform activity continues even after the electrical stimulation has ended, and becomes permanent, producing acute seizures that can lead to hippocampal neuronal loss and gliosis (Cibula & Gilmore, 1997). Pathways in the limbic system and temporal lobes are particularly susceptible to kindling. The theory of kindling, originally described by Goddard (1967) (as cited in Acharya, 2002) has been extensively studied for over 30 years in animals, but has not been directly demonstrated in humans, and therefore, its relevance to humans remains controversial (Acharya, 2002; Cibula & Gilmore, 1997). In animals, kindling seems to develop and evolve more slowly in more advanced species, such as primates. It is possible that kindling to the point of spontaneous seizures does not occur in humans; however, the cumulative effects of repeated seizures may contribute to some features of TLE (Acharya, 2002).

A type of secondary epileptogenesis is called mirroring in which the secondary epileptogenic zone is located directly opposite of the primary epileptogenic zone. The definition of secondary epileptogenesis suggests that for some individuals, the natural
history of epilepsy may be progressive, and repeated seizures may promote additional seizures (Cibula & Gilmore, 1997).

There are three stages of secondary epileptogenesis, as reported by Acharya (2002). The first stage is the “induction” stage of the primary epileptic focus in which the application of repeated electrical current, which has come to be known as “kindling” is achieved. If the dependent focus is not removed or treated, seizures begin to develop independently at the second site. This is considered the “intermediate” stage. At this time, if the primary focus is removed, secondary activity will resolve, but it will take time for recovery to occur. With continued exposure to the primary focus, clinical seizures arise from the secondary site independently, and this is known as the “independent” stage of epileptogenesis. This sequence of events produces new foci, but surgical resection of the primary focus or the use of antiepileptic medication may hinder the growth of new foci (Cibula & Gilmore, 1997).

Morrell (1989) reported that while a significant number of patients with focal epilepsy develop secondary epileptogenic lesions, this is rare in patients who have MTLE with hippocampal sclerosis because antiepileptic drugs (AEDs) control secondary generalization much better than they control partial seizures (Wieser, 2004). Secondarily generalized seizures in these patients tend to be caused by poor AED compliance or deficient sleep habits, and may correlate with the extent of the lesion (Wieser, 2004).

Epileptic discharges originating in the temporal lobe frequently invade an ipsilateral frontal region and may incur some potentially epileptogenic properties, even if many seizure onsets indicate a main temporal epileptogenic region (Adam et al., 1994). Focal epileptic discharges can eventually lead to neuronal dysfunction in areas remote
from the seizure focus, thereby contributing to further impairment of temporal lobe functions (Cendes et al., 1997). This underscores the importance of rigorous seizure control and consideration of earlier surgical intervention.

Patients with a long history of seizures prior to surgery are more likely to develop seizures after surgery, suggesting that secondary epileptogenesis may develop at distant sites after years of uncontrolled seizures, and may be related to tissue not resected during surgery (Eliashiv et al., 1997).

In conclusion, chronic seizures may cause secondary remote dysfunction that might eventually lead to contralateral or ipsilateral epileptogenesis. Anti-epileptic medications or surgical treatment may allow some recovery of function in the affected tissue by eliminating seizures. Early and aggressive treatment may help prevent further dysfunction once seizures have already compromised neuronal tissue. Should drug therapy prove to be ineffective, early resection of epileptogenic tissue might prevent more extensive dysfunction in other tissues and allow some recovery of already dysfunctional tissues (Hugg et al., 1996).

**Neurometabolic compromise (NAA/Cr).** A defect of metabolism offers a possible explanation for extratemporal deficits in patients with temporal lobe epilepsy. Neurometabolic compromise occurs as a result of disruption of neuronal metabolites caused by seizure activity and has been detected in areas outside of the epileptogenic temporal zone. N-acetylaspartate (NAA) and creatine (Cr) are neural metabolites: NAA indicates the metabolic activity of the neurons and Cr has the most stable concentration of the metabolites. The ratio of NAA to Cr (NAA/Cr) reflects the quantitative value of NAA and is typically considered an index of the NAA level (Kikuchi, Kubota, Hattori,
Oya & Mikuni, 2001). Changes in NAA/Cr reflect local alterations in glial or neuronal metabolism. NAA/Cr ratios are low (decreased) in patients with temporal lobe epilepsy and are markers of both local and remote physiological dysfunction associated with ongoing seizures (Cendes et al., 1997). Magnetic resonance spectroscopic imaging (MRSI) is a useful method of detecting neuronal damage in patients with TLE based on reduced signals from N-acetylaspartate (NAA), which is localized exclusively in neurons (Cendes et al., 1997).

*Magnetic resonance spectroscopy (MRS).* Proton magnetic resonance spectroscopic imaging ($^1$H MRSI) is a non-invasive method of estimating brain metabolites and has proven to be a valuable tool in the study of patients with temporal lobe epilepsy (Simister et al., 2002). In temporal lobe epilepsy several studies have already shown a close relationship between MRS abnormalities and the seizure focus (Kikuchi, et al., 2001). Neuronal loss and gliosis characterize hippocampal sclerosis (Cendes et al., 1997; Hugg et al, 1996; Martin, Sawrie et al., 1999). As neuronal loss is associated with reduced NAA and gliosis is associated with increased Cr, $^1$H MRSI can reliably detect epileptogenic focus in TLE (Hugg et al., 1996). It has also proven to be an effective instrument for determining extent and lateralization of neuronal damage (Garcia et al., 1997; Martin, Sawrie et al., 1999).

Several research studies have provided evidence to suggest that $^1$H MRS may be more sensitive to neurocognitive function than other magnetic resonance measures of brain structure (Martin, Sawrie et al., 1999; Sawrie et al., 2000; Tasch et al., 1999). Previous research has shown the clinical utility of $^1$H MRS imaging in efforts to detect subtle neurochemical abnormalities not detected with standard quantitative MRI
techniques. Conventional MRI can detect abnormalities in TLE in the hippocampus, amygdala, or both (Tasch et al., 1999). Volumetric analysis (MRIvol) can detect reduced volume of mesial temporal lobe structures in most patients with mesial temporal sclerosis; however, there are still a significant proportion of patients with TLE in whom MRI changes cannot be detected (Tasch et al., 1999). Unlike conventional MRI, which provides structural information based on signals from water, MRSI provides chemical information. It provides a non-invasive examination of regional chemical composition (Tasch et al., 1999).

Volumetry versus spectroscopy. MRI volumetry has been helpful in identifying the relationship between hippocampal atrophy and surgical outcome in MTLE (Jack, Theodore, Cook & McCarthy, 1995). Hippocampal atrophy was found to correlate significantly with hippocampal field neuronal loss and glial cell proliferation when measured by MRI volumetrics (Luby, Spencer, Kim, Delanerolle, & McCarthy, 1995). Tasch et al. (1999) found that although MRSI and MRIvol results are often concordant and work well together in the presurgical evaluation of patients with temporal lobe epilepsy, MRSI is a more sensitive indicator of neuronal dysfunction and thus better able to detect abnormalities than MRI volumetry. In a study by Tasch et al. (1999), a correlation between duration of seizures and NAA/Cr was detected using MRSI both ipsilateral and contralateral to the seizure focus. MRIvol, however, was unable to detect a contralateral correlation indicating dysfunction. In a study of the cognitive effects of hippocampal sclerosis, $^1$H MRS was more sensitive to episodic verbal memory function than was MRI volumetrics (Sawrie et al., 2001). The lack of a strong correlation between MRIvol and $^1$H MRSI suggests that the two technologies are measuring different
processes, however, meaningful information regarding cognitive function can be derived from both measures (Sawrie et al., 2001; Tasch et al., 1999). MRI volumetry measures the total hippocampal volume, while the MRSI technique assesses regional changes (Kuzniecky et al., 1998). Kuzniecky et al. (2001) found that MRS metabolic measures do not reflect neuronal cell loss, but rather, they reflect neuronal and glial dysfunction. This supports the concept that the abnormal metabolic activity measured by MRS, and the hippocampal volume loss detected by MRI volumetry, do not have the same neuropathologic basis (Kuzniecky et al., 2001). Cendes et al. (1997) concluded that NAA and Cr abnormalities in TLE do not result solely from neuronal loss and gliosis, but can be reversible after post-surgical control of seizures.

**Extratemporal NAA/Cr ratios.** $^1$H MRS imaging has shown diminished NAA/Cr ratios that extend beyond the hippocampal region, to an area greater than previously noted in MRI volumetrics or imaging. Cendes et al. (1997) examined NAA metabolism using MRSI and found that neuronal dysfunction is widespread in the temporal lobe ipsilateral to the seizure focus in patients with TLE.

Previous studies of NAA metabolism using MRS measures have demonstrated that NAA is reduced not only in the ipsilateral, but also in the contralateral hippocampus of many patients with MTLE (Vermathen et al., 1997). Ipsilateral NAA/Cr is usually more reduced than contralateral (Tasch et al., 1999). Cendes et al. (1997) reported a higher frequency of bilateral NAA abnormalities than bilateral MRI abnormalities. The fact that structural abnormalities (i.e., hippocampal atrophy) and contralateral epileptogenic sites are less frequent than NAA abnormalities suggests that dysfunction
from seizure activity has less to do with neuronal cell loss than with neuronal metabolism (Cendes et al., 1997).

In a study by Tasch et al. (1999) using MRSI to measure NAA/Cr, a negative correlation was found between NAA/Cr and the duration of epilepsy in the temporal lobes ipsilateral and contralateral to the EEG focus (the greater the duration of epilepsy the lower the NAA/Cr ratio). This suggests that even when the seizures originate in only one temporal lobe, neuronal dysfunction may occur bilaterally in patients with TLE.

Normalization of extratemporal deficits. Several studies have found that normalization of extratemporal regions has occurred following successful control of seizures (Cendes et al., 1997; Hugg et al., 1996; Sawrie et al., 2001). NAA/Cr has been shown to recover ipsilaterally and contralaterally after resection of the seizure focus (Tasch et al., 1999). Abnormal preoperative levels of NAA/Cr have been shown to normalize in the contralateral hippocampus after successful epilepsy surgery (Sawrie et al., 2001).

In post-surgical patients with bilateral hippocampal abnormalities, Hugg et al. (1996) were able to demonstrate normalization of Cr/NAA in the unoperated contralateral tissue following cessation of seizures.

Several studies have failed to find a significant association between the degree of hippocampal atrophy and hippocampal metabolite ratios. Therefore, it is thought that NAA may be a marker for neuronal function rather than structure (Sawrie et al., 2001). The observation that the relative NAA concentration in the temporal lobe increases after surgical therapy in patients who become seizure free indicates that the dysfunction was
transient and merely a response to neuronal stress rather than a result of neuronal loss or gliosis.

**Correlation of NAA/Cr to cognitive function.** In MRS studies, Gadian et al. (1996) reported that cell metabolism within the temporal lobe (represented as NAA/Cr ratios) is closely related to function, and disruption of cell metabolism has been associated with cognitive dysfunction. That finding was supported by Kikuchi et al. (2001) who reported significant correlations between NAA/Cr ratios and most of the neuropsychological tests for left temporal lobe function ipsilateral to the seizure focus. Significant correlations were also detected between the ratios in the right temporal lobe and the scores of all of the neuropsychological tests sensitive to the right hemisphere, except for Visual Reproduction subtest of the WMS-R (r = .353) (Kikuchi et al., 2001).

Levels of hippocampal NAA/Cr have been found to correlate significantly with episodic memory function, semantic memory function, and intelligence in patients with MTLE (Sawrie et al., 2001). In a study investigating $^1$H MRSI-detected MTL abnormalities, Rocchetta et al. (1995) found that right temporal lobectomy patients with contralateral metabolic abnormalities performed similarly on measures of verbal memory to left temporal lobectomy patients (as cited in Martin, Sawrie et al., 1999).

In contrast the these findings, Kikuchi et al. (2001) were unable to find significant correlations between the metabolic ratios in the left temporal lobe and the scores of any of the neuropsychological tests for the contralateral temporal lobe function except for the single WAIS-R subtest of Information (r = .416). As the WAIS-R Information subtest is typically considered a measure of lateral temporal lobe function, Kikuchi et al (2001)
suggested that hippocampal MRS reflects both hippocampal and lateral temporal function.

**Diaschisis.** Focal lesions are known to result in functional impairment at and around the damaged site. In addition, secondary clinical deficits have been known to occur to remote intact brain regions due to their disconnection from the damaged area. This concept of diaschisis, first theorized in the early 20th century, purports that damage to one part of the nervous system can have distant effects, and these effects are caused by loss of input to structures associated with the damaged area (Finger, Koehler, & Jagella, 2004). Disrupting the neuronal connections between regions produces temporary but distinct impairments of cognitive function. According to this theory, in TLE, damage to the temporal lobes could result in temporary deficits of connected structures, such as frontal lobes and parietal lobes. Such deficits could be ipsilateral and/or contralateral to the lesion site. The effects of diaschisis were thought to occur following acute or sudden onset (Finger et al., 2004).

Diaschisis can account for how an injury to one side of the brain can alter the functional activity on the other side of the brain. Because many structures in the brain are interconnected, whether directly or indirectly, all nervous structures can be affected by diaschisis, and its effects can be distant and widespread (Finger et al., 2004). Different parts of the nervous system vary in degree of susceptibility to diaschisis. In higher cognitive functions, older circuits, and those with more activation, appeared to be more resistant to diaschisis than newer, less used circuits (Finger et al., 2004).

It is difficult to discern whether deficits are caused specifically by the disruption of neural connections, because many brain changes can overlap within the first few days
after an injury. Such injuries can cause vascular changes, intracranial pressure, edema, neuroglial proliferation, cell death, changes in transmitter levels, and various other physiological changes, making it extremely difficult to isolate one event as the causal factor underlying this neurological effect (Finger et al., 2004).

One example of diaschisis is demonstrated in contralateral effects of focal seizures. It was speculated that the corpus callosum was the route through which the epileptogenic activity was transmitted. A study by Reggia (2004) was unable to replicate this effect, and determined that perhaps an indirect subcortical route may be the pathway through which transmission takes place. Studies of sodium amytal effects demonstrated mixed results. Using high-resolution hexamethyl propyleneamine oxime (HMPAO) SPECT de Silva, Duncan, Patterson, Gillham, and Hadley (1999) found hypoperfusion in the mesial temporal structures, suggesting that they were inactivated remotely by diaschisis. Another IAP study using SPECT found a decreased regional cerebral metabolism in both the medial and lateral temporal regions, suggesting that neuronal function was inactivated by diaschisis (Kim, Lee, Nam, Song & Lee, 1999). Yune et al. (1998) reported that ipsilateral thalamic hypoperfusion was not uncommon in TLE during interictal SPECT testing, and ascertained that corticothalamic diaschisis may play an important role. Further, in a study of cerebral glucose utilization using PET in patients with TLE, Khan et al. (1997) found decreased glucose uptake in ipsilateral temporolateral, ipsilateral temporomesial and bilateral frontolateral cortices. All patients showed decreased glucose uptake in contralateral temporolateral regions, while cerebellar diaschisis was observed in two patients (Khan et al., 1997). In contrast, findings by
Henry et al., (1994) resulted in the conclusion that hippocampal neuronal loss and diachisis could not account for the regional interictal hypometabolism of TLE.

Based on the variability of these studies and others, as well as variability among subjects within tests, diachisis is still a viable yet subjective theory for the remote cognitive effects of focal seizures.

**Summary and conclusions.** Cognitive deficits in temporal lobe epilepsy can extend to regions outside of the temporal lobes, especially the frontal areas. The reason for the extratemporal dysfunction is not well understood; however, several theories have been explored. Imaging studies provided evidence of remote dysfunction and studies of measures purported to examine frontal lobe ability were reviewed. Diaschisis, diffuse metabolic pathophysiology, secondary epileptogenesis, and undiagnosed seizure activity have been offered as possible explanations for these extratemporal deficits. While each of the theories provides viable causal possibilities, they have not resulted in a definitive answer.

Previous studies have demonstrated the existence of extratemporal deficits, but methodological differences and small patient groups leave room for further investigation. In the present study, a sample of patients with well-defined, unilateral temporal lobe epilepsy and clear evidence of seizure-free status for two years or more allows for a more precise examination of cognitive deficits arising outside of the epileptogenic zone. Although the study will not be able to provide the exact cause of the extratemporal deficits, or which one of the explanations is correct, the data should supply evidence supporting one explanation over the others.

### 1.7 Research Questions and Hypotheses
Past research has suggested that extratemporal cognitive deficits exist in individuals with unilateral temporal lobe epilepsy. The present study investigated this possibility by reviewing pre- and post-surgical neuropsychological test data to establish the presence and nature of such deficits. The study also examined whether left versus right temporal lobe epilepsy patients were more prone to extratemporal deficits and whether the nature of the extratemporal deficits differed for these two groups. The nature of extratemporal deficits was examined to determine if the deficits outside of the epileptogenic temporal lobe expressed a specific or selective effect on brain function or whether they involved a general suppression of brain integrity and functioning. A general suppression of brain integrity would have been represented by more diffuse impairment, such as deficits in abstraction, signs of perseveration, reductions in mental flexibility, or difficulty with psychomotor skills in the case of general frontal deficits. Post-surgical test results were reviewed to ascertain if normalization (recovery) of extratemporal deficits took place. The study attempted to discern if the extratemporal deficits arose from disrupted communication with the temporal lobes or whether the extratemporal effects were independent of the temporal lobe structures. If the deficits arose from functionally intact tissue that were dependent upon the epileptogenic temporal lobe and were expressing a transient burden from seizure spread (e.g., diaschisis), then these deficits should have recovered post-surgically.

Research Questions.

The following research questions were addressed:

1. Do extratemporal deficits exist in unilateral temporal lobe epilepsy when the concerns about undiagnosed seizures have been reduced, and are these
extratemporal deficits more probable in left versus right temporal lobe epilepsy patients?

2. If extratemporal deficits do exist, will the pattern of deficits suggest a general suppression of cognitive skills or more selective process?

3. If secondary cognitive effects of the seizures are selective, will they reflect a solely ipsilateral or contralateral process?

4. Does post-surgical recovery of extratemporal cognitive function take place in temporal lobe epilepsy patients?

5. If such recovery occurs, how does it inform us about the nature of the extratemporal deficits?

Hypotheses:

1. Extratemporal deficits will be present in patients with temporal lobe seizure disorder and will primarily involve frontal lobe regions ipsilateral to the epileptogenic zone in the left temporal epilepsy group, reflecting lower scores than controls on selective frontal lobe skills that place a premium on lexical and semantic word retrieval, such as the CVLT Total Learning index, COWA, Animal Naming, the BNT, and other executive function skills, such as Trails B, Digit Span Backwards, WCST Categories and Perseverative Errors indices, the Grooved Pegboard test, and Grip Strength.

2. Patients with left temporal lobe seizure disorder will have significantly lower scores than patients with right temporal lobe seizure disorder on the left temporal lobe measures of BDAE Auditory Comprehension, CVLT Retention, and Logical
Memory Retention, and on extratemporal measures of Trails B, Digit Span Backwards, COWA, Animal Naming, the CVLT Total Learning, WCST Categories and Perseverative Errors indices, BNT, the Grooved Pegboard test, Grip Strength, and Visual Reproduction Retention.

3. Extratemporal cognitive function will demonstrate post-surgical recovery of function as evidenced by higher scores in temporal lobe patients with good seizure control (seizure-free) compared to patients with poor seizure control on left frontal lobe measures, such as the COWA, Animal Naming, WCST Categories and Perseverative Errors, Trails B, Digit Span Backward, CVLT Total Learning, the Grooved Pegboard test, Grip Strength, and the BNT, and on measures of right temporal functions, such as the Wechsler Memory Scale Visual Reproduction subtests.

2. METHODS

2.1 Participants

The participants for this study (n=80) were selected from the patient archives of the Thomas Jefferson University Comprehensive Epilepsy Center in Philadelphia, PA. Participant files were selected based on the following criteria: a) age 18-50 years old, b) gender (male or female), c) with unilateral left or right simple or complex partial temporal lobe seizures (Table 1). Simple and partial complex seizures were confirmed by video/EEG monitoring, and magnetic resonance imaging (MRI) showed that lesions were consistent with a left or right temporal lobe focus. The neuropsychological data utilized for analyses were collected as part of a comprehensive pre-surgical and post-surgical
evaluation. Data on seizure outcome was acquired via post surgical interviews with patients and significant others. Patients were instructed to keep a log of seizure activity. Patients were examined within the first week of surgery, one month later, six months later, and at one year post-surgery. Only subjects who had reached two years post-surgery without seizures were included as the experimental group (n=61). The purpose of using subjects who are seizure-free for two years is two-fold: 1) to ensure that participants truly had focal unilateral seizures, and that other areas outside of the epileptogenic zone were not contributing to the dysfunction, and 2) to make sure the surgery removed the single epileptogenic area. Two years post-surgery is a reliable amount of time for determining future seizure status.

The following exclusion criteria were employed: 1) EEG evidence of multi-focal seizures, 2) diagnosis of seizure types other than simple or partial complex seizures, 3) recurrence of seizure activity at any time within two years following surgery.

Participants in the comparison group (n=19) consisted of temporal lobe epilepsy patients who met the same criteria as the experimental group, but continued to experience seizures within the two-year period following surgery.

2.2 Materials

Patient charts obtained from the Epilepsy Center at the Thomas Jefferson University Hospital for Neuroscience were reviewed for both presurgical and postsurgical neuropsychological test results. Demographics, medication use, epilepsy history, and surgical results were also examined.
2.3 Procedure and Measures of Cognitive Functioning

Participants were classified according to seizure outcome status and grouped accordingly in either the experimental or comparison group. Seizure outcome status was based on a grading scale of Classes I through IV. The Experimental group consisted of patients who were seizure-free for two years following surgical resection of temporal lobe lesions and were rated as Class I, the Seizure Free, or Good Outcome, group. The comparison group comprised patients who continued to experience seizures at any time within the two years following temporal lobectomies, and were rated Class II, III, or IV. The comparison group was designated Not Seizure Free, or the Poor Outcome group. Classes II through IV represented seizure outcomes that ranged from less than 3 seizures per year in the last year, to no appreciable change or seizure frequency is worse. Classes II through IV were collapsed into one group (Not Seizure-Free) due to their small group sizes.

Each patient received pre- and post-surgical neuropsychological examinations up to 6 months prior to surgery and one year following surgery, respectively. Intellectual functioning was tested using one of two editions of the Wechsler Adult Intelligence Scale, the Revised form (WAIS-R) or the third edition (WAIS-III) (Wechsler, 1981, 1997). The WAIS verbal subtests include Information, Vocabulary, Comprehension, and Similarities. The performance subtests of the WAIS include Picture Arrangement, Picture Completion, Arithmetic, Block Design, Object Assembly and Digit Symbol. Verbal, Performance, and Full-scale IQ were obtained. IQ measures are included in the demographic table (Table 1) according to seizure focus group. WAIS subtests included
in the analyses were Picture Completion, Picture Arrangement, and Block Design. Measures of academic achievement were derived from the Reading subtest of the Wide Range Achievement Test, revised edition (Jastak & Jastak, 1978). Academic Achievement measures were not included in the analyses, but WRAT-R Reading is listed in the demographics table according to seizure focus group as a baseline measure of premorbid functioning. Measures of temporal lobe functions are typically memory-related. They are material-specific, with the left (dominant) hemisphere specific for tasks of verbal memory and the right (non-dominant) hemisphere specific for non-verbal material. Verbal memory measures included subtests of the California Verbal Learning Test (CVLT) and CVLT-II (Delis, Kramer, Kaplan & Ober, 1987, 2000), as well as subtests from one of three editions of the Wechsler Memory Scale (WMS, WMS-R, WMS-III) (Wechsler, 1945, 1987, 1997). The CVLT is an auditory list learning paradigm which measures recall and recognition of verbally mediated material. CVLT measures used in this study include the number of words remembered in all five learning trials (Total Learning), and retention (or forgetting) of material over time (Long Delay Free Recall versus List A, Trial 5). The WMS Logical Memory subtests involve recall and recognition of short stories of verbally mediated material. Logical Memory measures used in this study include story material remembered immediately after presentation (Logical Memory I), and a retention index that reflects the rate of forgetting over the 30-minute period (Logical Memory Savings Index).

Measures of visual memory included the WMS Visual Reproduction subtests, the non-verbal counterpart to the Logical Memory subtests. The Visual Reproduction subtests measure the ability to reproduce and recognize simple geometric designs. The
subtests included in this study were memory for designs immediately after presentation (Visual Reproduction I) and the rate of forgetting, or retention of the material over a 30-minutre period (Visual Reproduction Savings Index).

Measures of dominant hemisphere function involved tests of language, such as The Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), Complex Ideational Material Test of the Boston Diagnostic Aphasia Examination battery (Goodglass & Kaplan, 1983), Semantic Fluency (Animal Naming) (Spreen & Benton, 1977), and Digit Span (forward) from the WMS. The Boston Naming Test (BNT) is a test of confrontation naming and a measure of semantic memory, requiring retrieval of long-term semantic knowledge. Complex Ideational Material (from the BDAE) is a measure of auditory comprehension that requires “yes” and “no” responses to four different paragraphs as well as several questions like, “Will a stone sink in water?” Animal Naming from the BDAE is a measure of semantic fluency. Patients were given one minute to name as many animals as possible without repeating any of them. The Digit Span (forward) test is a measure of immediate recall and attention.

Measures of right hemisphere function included the Rey Osterreith Complex Figure (Osterrieth, 1944). The Rey Osterreith Complex Figure (ROCF) is a test of both visuospatial constructional ability and visual memory. Patients were given a complex design to look at and instructed to reproduce the design as carefully as possible. Immediately after copying the design, the stimulus was removed and patients were told to draw the design from memory. Scores were based on accuracy and placement of various aspects or units of the figure. A score of 0, 0.5, 1, or 2 was assigned to each unit.
according to specific criteria provided for the test. A raw score was then obtained, based on the sum of each unit score.

Measures of Executive Function included the Wisconsin Card Sorting Test (WCST) (Heaton, 1981), Verbal Fluency (FAS) from the Controlled Oral Word Association Test (Spreen & Benton, 1977), Trail Making Test, part B (Reitan & Wolfson, 1985), and Digit Span (backwards) from the WMS. For the purposes of this study, the Boston Naming Test will be evaluated as an executive function measure due to its reliance on frontal lobe mediation. The WCST is a measure of mental flexibility, problem solving, concept formation, and perseverative tendencies. In this test, patients were required to sort cards according to categories based upon color, shape, and number relying solely on feedback of “correct” or “incorrect” responses. Indices within the WCST include Categories Achieved and Perseverative Errors. The COWA verbal fluency test is a measure of word production based on a given letter (e.g., F-A-S) within a one-minute time period. Certain restrictions are placed on the response options, such as the inability to repeat words, use proper names, or duplicate words by adding endings, such as “ing”. Although the COWA is considered a language test, it is also a frontal function due to its mediation by the prefrontal cortex and its sensitivity to frontal lobe damage. The Trail Making Test, Part B is a measure of psychomotor speed that involves mental flexibility, visual search, sequencing and cognitive set shifting. The task requires an examinee to connect numbers and letters in alternating order that are randomly positioned on a page. Digit Span backwards is a task that requires the repetition of digits in reverse order from the order of presentation. The digit span increases in length from 2 to 8 digits. It is a measure of working memory, attention, and mental flexibility.
2.4 Data Analyses

All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS Version 17.0 for Windows). To determine overall performance differences, group scores were compared by means of one-sample t-tests, independent t-tests, repeated measures analyses, and one-way analyses of covariance (ANCOVAs).

To determine impairment of cognitive function, scores on test measures were compared to normative data based on age, education, and gender of participants. Scores were converted to z-scores and analyzed using one-sample t-tests. Impairment was indicated by scores significantly lower than controls, except for WCST Perseverative Errors Index, Grooved Pegboard test, and Trails B for which higher scores indicated impairment.

Independent t-tests were used to compare performance of left versus right temporal lobe patients. An Analysis of Covariance was conducted to test rival explanations for the results, using seizure focus groups as between-subject variables and duration of epilepsy, seizure outcome, education, and age as covariates. In cases where significant effects were indicated, post hoc Bonferroni corrections for multiple tests were conducted to minimize the chance of Type I error.

Various repeated measures analyses of variance were conducted to analyze pre- and post-surgical test performances, with seizure outcome group and seizure focus groups as between-subjects variables. A repeated measures analysis of covariance included duration of epilepsy as a covariate. For measures requiring non-parametric analyses, one-sample Kolmogorov-Smirnov Z tests were conducted, and independent samples Mann-Whitney U-tests were used.
To determine change in cognitive status following surgery a discriminant function analysis was conducted using reliable change indices (RCIs). Individual test scores on each measure were converted to difference scores that were calculated by subtracting pretest scores from post-test scores. These difference scores were then compared to Reliable Change Indices (RCI’s) that were developed by Hermann et al. (1996) and Sawrie, Chelune, Naugle, and Luders (1996). Scores were designated as improved, declined, or no change based on where they fell within or outside of the RCI range. The discriminant function analysis was performed to determine the pattern of cognitive performance that best discriminated the seizure free and poor-seizure control groups.

3. RESULTS

Table 1 depicts the relevant demographic and clinical data for the left and right temporal lobe seizure focus groups. No significant group differences were revealed, although a trend was indicated for the level of education to be higher in the left seizure focus group. Anti-convulsant medications present in the sample are shown in Table 2. Table 3 provides the histopathic breakdown of participants, and Table 4 provides a breakdown of MRI findings according to left and right temporal seizure focus group.

**Hypothesis 1:** Extratemporal deficits will be present in patients with temporal lobe seizure disorder and will primarily involve frontal lobe regions ipsilateral to the epileptogenic zone in the left temporal lobe epilepsy group, reflecting lower scores than controls on selective frontal lobe skills that place a premium on lexical and semantic word retrieval, such as the CVLT Total Learning index, COWA, Animal Naming, the BNT, and other executive function skills, such as Trails B, Digit Span Backwards, WCST.
Categories and Perseverative Errors indices, the Grooved Pegboard test, and Grip Strength.

Neuropsychological test measures were converted to Z-scores, and One-Sample t-tests were conducted on left seizure focus groups to determine the existence and extent of impairment in patient groups as compared to normal controls (Table 5). Mean scores that were significantly less than zero were considered impaired. Various test measures, such as the WCST indices, Trails B, Logical Memory I and II, and Grooved Pegboard test for the non-dominant hand, demonstrated skewed distributions violating the assumption of normality. On these measures, non-parametric One-Sample Kolmogorov-Smirnov Z tests were conducted to determine group differences.

The following measures of frontal lobe function revealed significant impairment: the BNT, COWA, Animal Naming, CVLT Total Learning, WCST Categories, and the Grooved Pegboard test for the dominant hand. After applying Bonferroni corrections for multiple tests, significance remained for all measures.

A trend was seen for Grip Strength for the non-dominant hand, with patients performing better than controls. No significant group differences were found on Digit Span Backwards, WCST Perseverative Errors, Trails B, the Grooved Pegboard Test for the non-dominant hand or Grip Strength for the dominant hand.

The contralateral temporal lobe measures of Visual Reproduction I and II were significantly impaired, but VR-I but lost significance following Bonferroni corrections. VR-II remained significantly impaired relative to controls.

Three subtests of the Wechsler Adult Intelligence Scale (Picture Completion, Picture Arrangement, and Block Design) were examined. Scores were significantly
lower than controls on the Picture Completion subtest. No significant group differences were found on the Picture Arrangement or Block Design subtests. On other non-frontal-lobe measures of language, memory, executive function, and visuospatial skills, the left seizure focus group performed significantly worse than controls on BDAE Auditory Comprehension, CVLT Long Delay Free Recall, Digit Span Forward, and the Rey-Osterrieth Complex Figure Copy. After applying Bonferroni corrections, these measures all remained significant except for Digit Span Forward. No significant group differences were found on the non-frontal lobe measures of Logical Memory I or II.

**Hypothesis 2:** Patients with left temporal lobe seizure disorder will have significantly lower scores than patients with right temporal lobe seizure disorder on the left temporal lobe measures of BDAE Auditory Comprehension, CVLT Retention, and Logical Memory Retention, and on extratemporal measures of Trails B, Digit Span Backwards, COWA, Animal Naming, CVLT Total Learning, the WCST Categories and Perseverative Errors indices, BNT, the Grooved Pegboard test, Grip Strength, and Visual Reproduction Retention.

Independent t-tests were conducted to examine differences between seizure focus groups (Table 6). On the left temporal lobe measures, significant group differences were found on CVLT Retention (Long Delay Free Recall versus Trial 5) and on Logical Memory Retention. No group differences were detected on Animal Naming or BDAE Auditory Comprehension. After post-hoc Bonferroni corrections, the CVLT and Logical Memory retention measures remained significant. For these measures, the left temporal lobe seizure focus group performed significantly worse than the right temporal lobe seizure focus group.
Analysis of extratemporal frontal and contralateral right temporal measures revealed significant differences on the frontal lobe measures of CVLT Total Learning, the BNT, and Grip Strength for the non-dominant hand. There were no significant differences between left and right seizure focus groups on the COWA test, Trails B, Digit Span Backwards, the WCST Categories or Perseverative Errors indices, Grooved Pegboard tests, or Grip Strength for the dominant hand. Differences were also not found on the contralateral right temporal lobe measure of Visual Reproduction Retention. Following Bonferroni corrections, significance was not upheld on any of the extratemporal measures.

Other measures were examined, such as the Picture Completion, Picture Arrangement, and Block Design subtests from the WAIS, and the Rey-Osterrieth Figure Copy, and no significant differences were noted between left and right seizure focus groups.

An Analysis of Covariance was then conducted on the significant dependent measures with Duration of Epilepsy, Seizure Outcome, Education, and Age as covariates (Table 7). There were no significant main effects of Duration of Epilepsy, Age, Education, or Seizure Outcome on the CVLT Retention measure. Age demonstrated a significant main effect on the Logical Memory Retention measure. Seizure focus continued to demonstrate a significant effect on the two retention measures, even after applying post-hoc Bonferroni corrections.

Hypothesis 3. Extratemporal cognitive function will demonstrate post-surgical recovery of function as evidenced by higher scores in temporal lobe patients with good seizure control compared to patients with poor seizure control on frontal lobe measures,
such as the COWA test, Animal Naming, WCST Categories and Perseverative Errors, Trails B, Digit Span Backward, CVLT Total Learning, the Grooved Pegboard test, Grip Strength, and the BNT, and on measures of right temporal functions, such as the Wechsler Memory Scale Visual Reproduction subtests.

A Repeated Measures Analysis of Variance was conducted to evaluate pre- and post-surgical test performance differences between outcome classification groups (Tables 8 and 9). The Seizure Outcome variable identified good versus poor seizure control groups and served as the Between Subjects variable.

3.1 **Frontal Functions**

3.1.1 **Pre- versus post-surgical test time.**

The main effect of Pre versus Post-surgical testing was first examined on measures of frontal function. The CVLT Total Learning subtest and the Grooved Pegboard test for the non-dominant hand demonstrated significant group differences. On the Grooved Pegboard test for the non-dominant hand, scores indicated better performance at post-testing; scores were better at pre-testing on the CVLT Total Learning subtest. Similarly, a trend was noted on the BNT for scores to be higher at pre-testing. No significant differences were found between pre- and post-surgical scores on the COWA, WCST Categories or Perseverative Errors indices, Trails B, Digit Span Backwards, Grooved Pegboard for the dominant hand, or Grip Strength. After applying Bonferroni corrections, only the Grooved Pegboard test for the non-dominant hand remained significant.
3.1.2 Seizure outcome.

The main effect of Seizure Outcome was then examined on frontal lobe measures, and significant differences were found between the good seizure control group (Seizure-Free) and the poor seizure control group (Not Seizure-Free) on the Boston Naming Test. In addition, a trend was revealed on Digit Span Backwards. For both of these tests, the scores of patients with good seizure control were higher than the scores of patients with poor seizure control. Following post-hoc corrections, no significant group differences remained. No differences between seizure outcome groups were detected on WCST-Categories or Perseverative Errors indices, the COWA, Trails B, CVLT Total Learning, Grooved Pegboard, or Grip Strength tests.

3.1.3 Interaction effects.

The interaction of Seizure Outcome group and Pre and Post testing yielded a significant effect on the WCST Perseverative Errors index. For this measure, scores improved after surgery in the good seizure control group and declined following surgery in the poor seizure outcome group. Significance remained on the WCST PE index after Bonferroni corrections. There were no other significant interaction effects or trends noted on frontal lobe measures.

3.2 Right Temporal Lobe Functions

Repeated Measures ANOVAs were also conducted to examine the effects of seizure outcome (good versus poor seizure control) on measures of right temporal lobe function, such as the WMS Visual Reproduction Immediate Memory (VR-I) and Retention (VR Savings) subtests.
3.2.1 Pre- versus postsurgical test time.

There were no significant group differences on VR-I or VR Retention for the main effect of Pre- versus Post Surgery.

3.2.2 Seizure outcome.

Significant differences were demonstrated on the Visual Reproduction Retention measure for the main effect of Seizure Outcome, on which the good seizure outcome group performed better than the poor seizure outcome group. There were no significant differences between Seizure Outcome groups on the Visual Reproduction measure of immediate memory (VR-I).

3.2.3. Interaction effects.

There were no significant interaction effects or trends on measures of right temporal function.

3.3 Other Measures

3.3.1 Pre- versus postsurgical test time.

Other measures were examined for group differences. For the Main effect of pre- and post-surgical testing, significant differences were observed on Logical Memory I, CVLT Retention, and CVLT Long Delay Free Recall. Scores were significantly higher at pretesting. The WAIS Block Design subtest also revealed significant pre and post-test scores differences. Scores were significantly better at post-testing. After post-hoc corrections, only the CVLT Long Delay and Block Design measures retained their significance.

3.3.2 Seizure outcome.
A significant main effect for Seizure Outcome was seen on the CVLT Retention measure and the WAIS Picture Completion subtest. A trend was noted on the WAIS Block Design subtest and the CVLT Long Delay Free Recall measure. No significant findings for the main effect of Seizure Outcome remained for these measures following Bonferroni corrections. The measures of BDAE Auditory Comprehension, Rey-Osterrieth Figure Copy, Digits Forward, Logical Memory Retention, and Picture Arrangement were not statistically significant for this effect.

### 3.3.3 Interaction effects.

A significant interaction effect of Seizure Outcome at Pre- and Postsurgical test times was demonstrated for the Logical Memory-I measure. Trends were indicated for the CVLT Retention and Logical Memory Retention subtests. Following Bonferroni corrections, no significant group interaction effects remained on non-frontal lobe measures. In addition, there were no significant interaction effects seen on BDAE Auditory Comprehension, Rey-Osterrieth Figure Copy, or the WAIS Picture Completion, Picture Arrangement, or Block Design subtests.

To examine the effects of temporal lobe Seizure Focus group (left versus right) on Seizure Outcome status (good versus poor), a Repeated Measures Analysis of Variance was conducted with Seizure Focus as an additional Between-Subjects variable (Tables 10 and 11).

The main effect of Pre- and Post testing remained significant on the Grooved Pegboard test for the non-dominant hand. This frontal lobe measure demonstrated higher scores at post-testing than at pre-testing. The temporal lobe measure, CVLT Long Delay Free Recall, also remained significant, but scores were higher at pre-surgical testing than
at post-surgical testing. The WAIS Block Design subtest also remained significant, but higher scores were achieved at post-surgical testing.

The main effect of Seizure Outcome Status remained significant for the WAIS Picture Completion subtest, with the good seizure outcome group performing better than the poor seizure outcome group.

An interaction trend of Pre and Post, Seizure Focus, and Seizure Outcome Status was noted on the CVLT-LDFR test. In the left seizure focus group, the good outcome group performed better than the poor seizure outcome group at both pre- and post-surgical testing. In addition, both the good and poor seizure outcome groups performed better at pre-surgical testing than at post-surgical testing. In the right seizure focus group, the poor seizure outcome group performed better than the good seizure outcome group at pre-surgical test. The opposite was true at post-surgical testing. In addition, both seizure outcome groups received higher pre-surgical than post-surgical scores on the CVLT-LDFR index.

A Discriminant Function Analysis was performed on Reliable Change Indices to assess the predictive power of the neuropsychological variables for discriminating between seizure focus and outcome groups (Tables 12 and 13). The Total Learning subtest of the CVLT revealed significant group predictability, with seizure focus demonstrating the strongest predictive power, followed by seizure outcome and then duration of epilepsy. For this measure, 68.3% of the cases were correctly classified.

4. DISCUSSION

The primary goal of the present research was to establish the presence and nature of extratemporal cognitive deficits in unilateral temporal lobe epilepsy. Three hypotheses
focused on various aspects of the existence of these deficits, such as the brain regions predicted to be impaired, pattern of impairment (selective or general process), and normalization patterns.

4.1 Summary of Findings

Only partial support was indicated for the three hypotheses. Extratemporal deficits were established in frontal lobe and in contralateral temporal lobe regions. The pattern of deficits did not reflect a selective process, as impairment was not specific to measures of verbal and semantic word retrieval. However, a strong bias towards left frontal measures of word retrieval was seen. Other executive function measures involving concept learning and fine motor skills were also impaired indicating a more general suppression of cognitive skills. Seizure focus was not a factor in the presence of extratemporal deficits, as there were no significant differences between seizure focus groups on extratemporal measures. Recovery of function did not occur in general, as many post-surgical scores reflected declines rather than improvements.

4.2 Hypothesis 1

The first hypothesis stated that cognitive deficits would be present in regions outside of the focal temporal lobe seizure location. The analysis focused on the ability to detect ipsilateral frontal and contralateral right hemisphere deficits among the left temporal lobe epilepsy patients. Neuropsychological test scores of the left temporal lobe epilepsy group were examined, and it was hypothesized that the frontal lobe deficits would involve regions ipsilateral to the epileptogenic zone in the left temporal lobe. These deficits would be reflected by impaired scores on frontal lobe skills that place a premium on lexical and semantic word retrieval, suggesting a selective effect on brain
function rather than a general suppression of cognitive skills. The data partially supported this hypothesis.

In support of the hypothesis, extratemporal deficits were established in frontal lobe regions ipsilateral to the epileptogenic zone. Measures of verbal and semantic fluency, visual naming, and word acquisition and retrieval were impaired in patients with left temporal lobe seizure disorder.

Although these frontal lobe deficits reflect skills that place a premium on lexical and semantic word retrieval, other frontal lobe measures of concept learning and fine motor skills using the dominant hand were also impaired. This is in contrast to the hypothesis, as it suggests that the nature of the deficits reflects a more general suppression of brain integrity rather than a selective process. Deficits were not specific to measures of word retrieval, and a more diffuse impairment of frontal lobe functions was identified. This general frontal effect suggests that the deficits are independent of temporal lobe functioning. They do not arise from disrupted communication with the dysfunctional, epileptogenic temporal lobe (diaschisis), nor do they reflect a breakdown in any specific cognitive network interacting with the temporal lobe. Rather, they indicate the build-up of separate and independent dysfunction.

Support for the hypothesis was not found on frontal lobe measures involving integrity of motor functioning with the dominant hand, fine motor functioning with the non-dominant hand, psychomotor speed, working memory, or perseverative tendencies.

Non-frontal lobe test measures were also examined in order to identify patterns of function. Measures of auditory comprehension, visuospatial constructional ability, visual perception, and verbal retention of word lists were significantly impaired when compared
to controls. Impairment was also found on a measure of delayed visual memory, indicating contralateral temporal lobe effects.

The general prediction that extratemporal deficits exist in focal temporal lobe epilepsy patients was supported by these analyses. The pattern of deficits indicated impairment of frontal lobe regions, specifically, but not exclusively those involved in word retrieval. Frontal lobe measures that did not reveal significant impairment were unrelated to word retrieval. Nevertheless, they presented a dilemma, as past research found these measures to be impaired in the left temporal lobe epilepsy population (Hermann & Siedenberg, 1995; Martin et al., 2000; Kim et al., 2003). There are several possible explanations for the lack of impairment detected in these measures. One possibility is that the small sample sizes magnify the effects of outliers and deviant scores. In most of the non-significant frontal lobe measures, there are substantial outliers that create large standard deviations and distort the distribution of the scores.

Another possibility is the variation in seizure propagation patterns of temporal lobe epilepsy patients that can result in diverse cognitive deficits. Hermann et al. (1991) proposed that the variation in the temporal lobe epilepsy population might be related to the pattern of seizure spread in the cortex, interictal electrophysiological abnormalities, or other factors. Adam and colleagues (1994) suggested that frontal regions are more frequently invaded than the contralateral temporal regions, but acknowledged that propagation pathways are variable and can deviate from the pattern. Lieb et al. (1991) suggested that at least nine patterns of seizure spread have been demonstrated. According to Spencer et al. (1987), the pattern of seizure spread may even vary in the same patient. It is possible that our patient group varied in their seizure propagation
patterns, which altered the pattern of deficits typically seen in temporal lobe epilepsy
patients.

Finally, epilepsy can be caused by a variety of neurological conditions. Depending
upon the etiology of the seizure disorder, variations in brain morphology can occur,
resulting in distortions of functional domains. Structural lesions associated with temporal
lobe epilepsy include malformations, tumors, familial and metabolic disorders,
cerebrovascular accidents and trauma, inflammatory and infectious illnesses, and
hippocampal sclerosis (Vintners et al., 1993).

The diverse neuropathology of temporal lobe epilepsy may play a role in the
variability of neuropsychological test results (Paradiso et al., 1993). In a sample of
temporal lobe epilepsy patients with diverse pathology, mean differences can vary
extensively. The rapid spread of seizure discharges to several brain areas may account
for some of the neuropsychological variability, as both cortical development and mental
functions are negatively influenced by seizures (Motamedi & Meador, 2003). Differing
patterns of deficits would likely take place in terms of brain regions and effects, resulting
in a variation of mean scores on test measures.

Although some studies have shown that the etiology of epilepsy has no significant
impact on cognitive performance (Grafman, Jonas, & Salazar, 1992; Upton & Thompson,
1997), Sailing and associates (1993) found that memory test performance in TLE varies
as a function of the underlying neuropathology.

Early onset of epilepsy has been associated with a greater likelihood of structural
abnormalities, and more than half of our study sample (51.2%) had epilepsy onset prior to
eight years of age. Hermann et al. (2002) found that patients with childhood-onset
temporal lobe epilepsy (mean onset age, 7.8 years) exhibited widespread compromise in neuropsychological performance and substantial reduction in brain tissue volumes extending to extratemporal regions compared with healthy controls and late-onset temporal lobe epilepsy patients (mean onset age, 23.3 years). It has also been proposed that early epilepsy onset may produce a reorganization of the cognitive architecture, and a reassignment of the functional features of specific brain areas (Patrikelis, Angelakis, & Gatzonis, 2009).

Another important feature of structural abnormalities, including gyral and sulcal curvature, cortical depth, and total cortical surface area, is that they generalize despite the focal nature of the primary epileptic process (Oyegbile, Hansen et al., 2004). Oyegbile, Hansen and colleagues (2004) found that these abnormalities were associated with increasing chronological age and cognitive performance, and with other morphometric measurements (i.e., surface cerebral spinal fluid).

These developmental malformations of the cerebral cortex are increasingly being recognized as an important pathologic substrate in patients with refractory epilepsy (Martin, Dowler et al., 1999). It is highly possible that these variations in brain structure and distortions of functional domains could result in atypical patterns of test scores on neuropsychological measures.

4.3 Hypothesis 2

The second hypothesis addressed the laterality effects of extratemporal deficits. The purpose of this hypothesis was to determine whether extratemporal deficits were more likely to be found in left or in right temporal lobe seizure focus groups. It was predicted that patients with left temporal lobe seizure disorder would be more
compromised on tasks normally associated with left temporal lobe function, but in addition, on tasks associated with frontal regions. Significant findings of dysfunction on temporal lobe measures of verbal retention of words lists and stories, and visual retention of designs would corroborate previous studies demonstrating laterality effects of material-specific deficits and in identifying contralateral deficits.

Supporting this prediction, the left temporal seizure focus group performed significantly worse on verbal retention measures. These results concur with previous research purporting that measures of verbal memory are associated with the left temporal lobe, confirming that the data are showing material-specific deficits (Milner, 1972).

The analysis did not support the prediction that the left hemisphere measure of auditory comprehension would be more impaired in left temporal patients than in right temporal patients. A review of group means revealed scores that were almost equal in left and right seizure focus groups. The fact that this measure was not more impaired in the left group than in the right group is puzzling, since auditory comprehension is a language function, which is usually associated with the left hemisphere in right-hand dominant patients. It is possible that mixed or atypical language dominance may be a factor in these results. In a small portion (6%) of the general population, atypical, either right or bilateral, representation of language function can be observed. Atypical language representation seems to be more frequent in epileptic patients; estimates of right-handers who have right-hemisphere language dominance ranges from 4-37% (Brázdil, Zákopcan, Kuba, Fanfrdllová, & Rektor, 2003). It is widely acknowledged that following extensive damage to the left hemisphere sustained in early childhood, language functions are likely to reorganize and develop in the right hemisphere. The reorganization of language
function to the right hemisphere may not only result in atypical patterns of deficits related
to language function, but may also compromise right hemisphere functions (Loring et al.,
1999). The lack of laterality effects on this measure may merely be an artifact of
cognitive reorganization resulting in mixed or atypical language dominance.

The prediction that extratemporal frontal and right hemisphere deficits would be
significantly greater in the left temporal group as compared to the right temporal group
was not supported. The majority of frontal lobe measures did not exhibit significantly
lower scores in the left temporal lobe group. Two exceptions involved measures of
verbal acquisition and visual naming. The effect size was small ($r=.16$) for the measure
of verbal acquisition, but was medium ($r=.37$) for the visual naming measure. These
measures did not retain significance after Bonferroni corrections.

The contralateral visual memory retention measure was not significantly more
impaired in left temporal lobe patients than in right temporal lobe patients. In addition,
no significant group differences were found on other measures associated with the right
hemisphere, including measures of visuospatial construction, perceptual organization,
and perceptual reasoning.

To examine the influence of other variables on the verbal memory retention
measures, an analysis of covariance was performed with duration of epilepsy, seizure
outcome, years of education, and age as covariates.

There were no significant effects of the covariates on the CVLT retention
measure, and together they accounted for only 3% of the unexplained variance. Age was
the only covariate that had a significant effect on the Logical Memory retention measure,
accounting for 8% of the unexplained variance. This suggests that Age contributed to the
effect on LM retention scores. The effect of seizure focus did not change as a result of
the covariates, accounting for 14% of the variance on each dependent measure. Seizure
focus had a significant effect on the verbal memory retention scores. Left temporal lobe
seizure focus patients were more likely to have lower scores on verbal retention measures
than right temporal lobe seizure focus patients.

The aim of hypothesis two was to determine if scores on extratemporal measures
would be lower in temporal lobe epilepsy patients with left seizure focus than in patients
with right seizure focus. Material specific memory measures established laterality
effects, but in general, significant hemispheric group differences were not found on
measures examining extratemporal regions; specifically, frontal lobe and contralateral
temporal lobe areas.

It is unclear whether these results are a function of the study sample, sample size,
hand dominance, or brain plasticity. Several of the measures, such as Trails B, Digit
Span Backwards, Grooved Pegboard test for the non-dominant hand, Grip Strength for
the dominant hand, and WCST Perseverative Errors index, were not significantly
impaired compared to controls, so it is possible that both the left and right seizure focus
groups could be equally unimpaired. Other measures, such as WCST-Categories, are
controversial as to localization within the frontal lobes. It has been purported that left
temporal lobe dysfunction after one year of age leaves sorting behavior relatively intact
(Strauss et al., 1993), and as less than 20% of our study sample experienced recurrent
seizures at or younger than age one, it is possible that they would have not experienced
the damaging cognitive effects of seizure activity on their WCST performance. Several
other studies have found no significant effects of laterality on the WCST and
performance on the WCST to be unrelated to TL function (Martin et al., 2000; Trennery & Jack, 1994). Although these arguments may be factors in the outcome of these analyses, it is likely that this sample did not experience the preferential left temporal seizure focus effects of seizure burden to extratemporal regions.

4.4 Hypothesis 3

The third hypothesis addressed post-surgical recovery of function. It was predicted that post-surgical scores would be significantly higher than pre-surgical scores for temporal lobe epilepsy patients having good seizure control (seizure-free patients) as compared to temporal lobe patients with poor seizure control (not seizure-free patients) on left frontal lobe measures and on measures of right temporal function. The analysis did not support this hypothesis.

It would be expected that only measures outside of the epileptogenic temporal lobe would demonstrate recovery of function following surgery, as they would not be directly affected by removal of lesioned tissue. Instead, they would benefit from the release of seizure burden, allowing any secondary effects of temporal lobe seizures to normalize. In contrast, measures of temporal function, within the epileptogenic zone, would be expected to decline following surgery.

4.4.1 Support for the hypothesis.

The only measure supporting this hypothesis was the WCST Perseverative Errors index, which demonstrated a significant interaction effect with pre versus post-surgical scores and seizure outcome. The good seizure outcome group improved significantly on post-surgical scores and performed significantly better than the poor seizure outcome group. Interestingly, the WCST-PE scores were not significantly impaired at either pre or
post-surgical test sessions compared to controls. A measure of verbal learning and memory also revealed an interaction effect for which the good seizure outcome group appeared to demonstrate post surgical recovery of function, but the effect became non-significant after Bonferroni corrections.

Support for the hypothesis was not found on any of the other measures in this analysis.

Pre- and Post surgery main effects yielded significant results on measures of motor dexterity for the non-dominant hand, verbal memory, and visuospatial and motor skills. Pre-surgical scores were better than post-surgical scores on all measures involving language function, including the measure of verbal memory. On both measures involving right hemisphere and frontal motor functions, scores improved following surgery. For these measures, however, there were no interaction effects indicating that the good seizure control group performed better at post-surgical testing than the poor seizure control group. Therefore, although recovery did appear to occur for these measures, it did not take place exclusively in the good outcome group.

The main effect of Seizure Outcome demonstrated significant differences between groups on measures of visual naming, visual retention of designs, and visual perception of details. For each of these measures, the good seizure outcome group performed better than the poor seizures outcome group, but there was no significant change in scores following surgery.

Examination of left temporal lobe measures revealed expected findings. Significant changes were indicated on verbal retention measures for the main effect of
pre and post-surgical test times. Changes involved declines in post-surgical test performance, most likely due to excision of tissue in the damaged temporal lobe.

4.4.2 Additional analyses.

After analyzing the pre and post-surgical test scores of seizure outcome groups, further Repeated Measures ANOVAs were conducted to examine the additional effect of seizure focus on frontal lobe measures. The significant interaction effect initially found of pre- and post-test times and seizure outcome status on the WCST-PE index lost significance when the seizure focus between-subjects variable was included. The interaction effect of seizure outcome and pre/post-test times yielded a medium to large partial eta squared effect size of 0.16 on the initial analysis. On the subsequent analysis that included seizure focus, the same interaction effect was reduced to a very small effect size of 0.05. No other significant effects were found on this measure. Therefore, with the inclusion of seizure focus, this measure would no longer support the hypothesis.

Including both seizure outcome and seizure focus as between-subjects variables did not alter the significant improvement in scores on the measure of manual dexterity using the non-dominant hand at postsurgical testing. In addition, it did not alter the significant finding indicating post-surgical improvement in scores on a measure of visuospatial perception.

4.4.3 Reliable change indices.

To minimize the possibility that postsurgical changes in test scores were due to practice effects, analyses were conducted using Reliable Change Indices (RCI’s). Scores were designated as Improved, Declined, or No Change based on where they fell within or outside of the RCI range. No change was found for the majority of measures.
Collapsing the data into two groups (Improved, Declined), a Discriminant Function Analysis was performed with seizure focus, seizure outcome, and duration of epilepsy as predictor variables. A test of verbal learning and acquisition was the only measure that demonstrated significant group predictability. It is believed that the large variation in group sizes may have been responsible for the lack of effects. Not surprising for this language measure, seizure focus group demonstrated the strongest predictive power, with the right temporal lobe seizure focus group exhibiting higher scores than the left temporal lobe seizure focus group. The ability to predict group membership was the weakest (-.228) for duration of epilepsy. This implies that, in this patient sample, the length of time a patient had epilepsy did not significantly influence whether or not improvement would occur.

4.4.4 Conclusions.

It is important to note that despite relatively no statistically significant improvements in test scores over time that would demonstrate recovery of function, case-by-case analyses of measures detected indications that improvement occurred. In the seizure-free group, scores on several of the extratemporal measures revealed non-significant improvement. Additionally, due to the large number of measures used in the analyses, even significant differences were eliminated following Bonferroni corrections. Effect sizes were not small in many of these measures.

There are several possible explanations for the findings in the above analyses. As previously mentioned, sample size, anomalies of seizure propagation patterns, the diversity of neurological conditions that cause epilepsy, and the resulting structural abnormalities and reorganization that can occur may account for the findings. The results
may have been just a function of the sample itself. Another sample may have produced very different results.

There were several limitations to the study. The sample size of the study was adequate, but measures varied in their group sizes. Some of them differed greatly when broken down into seizure outcome or seizure focus groups. This limited some of the analyses in terms of the measures that were useable. In this study, an attempt was made to include patients who were two years post surgery to ensure that resection was complete and that patients truly had unilateral focal seizures with no areas outside of the epileptogenic zone contributing to the dysfunction. As a result, it was quite difficult to find post-surgical participants that continued to experience seizures, and the seizure-free group significantly outnumbered the group that continued to experience seizures. A replication of this study including both normal controls and patients with poor seizure control as comparison groups would be interesting.

The nature of a retrospective study has its limitations regarding availability of raw data and reliance on limited information. In addition, several of the test measures required conversion to standardized scores because they were presented in different versions of the measure. Some of these scores had to be eliminated due to lack of information necessary to convert the scores.

This study demonstrated the erratic nature of disorders such as temporal lobe epilepsy and the lack of definitive patterns of cognitive deficits to be expected. In general, patterns of deficits are more likely in temporal lobe epilepsy than in other disorders. However, due to the nature of the illness, and the plethora of causes from which it arises, it is not surprising that variations of deficit patterns occur.
These findings have practical implications for the full spectrum of the epilepsy community: patients and their families, physicians and neurosurgeons, and the neuropsychologists performing assessments. Patients contemplating temporal lobe surgery would benefit from the a priori knowledge of what could be expected in terms of cognitive surgical outcomes. They would be able to assess whether the cognitive costs, such as memory loss and the possibility of executive function deficits, outweigh the benefits, such as relief from seizures. Families of patients would also be able to aid in the decision-making process according to the assistance they would be willing or able to provide.

Health-care providers who treat these patients, having a clear understanding of the cognitive impact associated with temporal lobe epilepsy, could better evaluate the postsurgical cognitive outcomes and consequences. This information may be a useful tool for determining the type and extent of surgical excision. In addition, this knowledge may be useful in planning cognitive rehabilitation.

Awareness of the possible cognitive dysfunction associated with temporal lobe epilepsy and the degree of compromise that unilateral focal seizures can elicit is crucial for proper assessment by neuropsychologists. It is important to explore all cognitive domains and brain regions when assessing patients with temporal lobe epilepsy, and unwise to assume that deficits will fit into a typical scenario of established cognitive deficits.
LIST OF REFERENCES


Upton, D., & Thompson, P. J. (1997). Neuropsychological test performance in frontal lobe epilepsy; the influence of aetiology, seizure type, seizure frequency, and duration of disorder. *Seizure, 6*, 443-447.


APPENDIX A: International Classification of Epileptic Seizures (ICES)

I. Partial Seizures

A. Simple partial seizures (without impairment of consciousness)
   1. With motor signs (i.e., focal motor, Jacksonian, versive, postural, phonatory)
   2. With somatosensory or special-sensory symptoms (i.e., visual, auditory, olfactory, etc.)
   3. With autonomic symptoms (i.e. epigastric sensation, pallor, sweating, papillary dilation)
   4. With psychic symptoms (usually occur with impairment of consciousness and more commonly experienced as complex partial seizures)
      - Dysphasic
      - Dysmnesic (e.g., deja-vu)
      - Cognitive (e.g., dreamy states)
      - Affective (fear, anger, etc.)
      - Illusions (e.g., macropsia)
      - Structured hallucinations

B. Complex partial seizures (with impairment of consciousness)
   1. Simple partial onset followed by impairment of consciousness
      - With simple partial features (as noted above)
      - With automatisms
2. With impairment of consciousness at onset
   - Impairment of consciousness only
   - With automatisms

C. Partial seizures evolving to secondarily generalized seizures (tonic-clonic, tonic, or clonic)
   1. Simple partial seizures evolving to generalized seizures
   2. Complex partial seizures evolving to generalized seizures
   3. Simple partial seizures evolving to complex partial seizures evolving to generalized seizures

II. Primarily Generalized Seizures

A. Absence seizures
   1. Absence
   2. Atypical absence

B. Myoclonic seizures
   1. Clonic seizures

C. Tonic seizures

D. Tonic-clonic seizures

E. Atonic seizures

III. Unclassified epileptic seizures
APPENDIX B: Classification of Epileptic Syndromes. Adapted from the Commission on Classification and Terminology of the International League Against Epilepsy (1989).

I. Localization-related (focal, local, partial) epilepsies and syndromes

A. Idiopathic
   1. Benign localization-related epilepsies of childhood
      a. childhood epilepsy with centrotemporal spikes (Rolandic seizures)
      b. childhood epilepsy with occipital paroxysms
   2. Autosomal dominant nocturnal frontal lobe epilepsy
   3. Familial temporal lobe epilepsy
   4. Primary reading epilepsy
   5. Hot water epilepsy

B. Symptomatic
   1. Chronic progressive epilepsia partialis continua of childhood
   2. Temporal lobe epilepsies
   3. Frontal lobe epilepsies
   4. Parietal lobe epilepsies
   5. Occipital lobe epilepsies

C. Cryptogenic
   1. Musicogenic epilepsy
   2. Eating epilepsy

II. Generalized epilepsies and syndromes

A. Idiopathic
1. Benign neonatal familial convulsions
2. Benign neonatal convulsions
3. Benign myoclonic epilepsy of childhood
4. Childhood absence epilepsy
5. Juvenile absence epilepsy
6. Juvenile myoclonic epilepsy
7. Epilepsy with tonic-clonic (grand mal) seizures on awakening
8. Other generalized idiopathic epilepsies

B. Symptomatic or Cryptogenic
   1. West syndrome
   2. Lennox-Gastaut syndrome
   3. Epilepsy with myoclonic-astatic seizures
   4. Epilepsy with myoclonic absences

III. Epilepsies and syndromes undetermined whether focal or generalized
   A. With both focal and generalized features
      1. Neonatal seizures
      2. Epilepsy with continuous spike-waves during slow wave sleep
      3. Landau-Kleffner syndrome (acquired epileptic aphasia)
   B. Without equivocal generalized or focal features
      1. Sleep generalized tonic-clonic seizures

IV. Special syndromes
   A. Situation-related seizures
      1. Febrile convulsions
2. Isolated seizures or isolated status epilepticus

3. Seizures occurring only with an acute metabolic or toxic event (e.g., alcohol, drugs, eclampsia hyperglycemia)
**APPENDIX C: Tables**

Table 1

Clinical and Demographic Data According to Seizure Focus

<table>
<thead>
<tr>
<th>Variable</th>
<th>Left Temporal Group (n=44)</th>
<th>Right Temporal Group (n=36)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
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<tr>
<td>Age</td>
<td>32.77</td>
<td>7.63</td>
<td>32.00</td>
</tr>
<tr>
<td>Education</td>
<td>13.75</td>
<td>2.15</td>
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<td>Age Seizure Onset</td>
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<td>9.12</td>
<td>11.24</td>
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<tr>
<td>Duration of Epilepsy</td>
<td>22.88</td>
<td>10.11</td>
<td>23.00</td>
</tr>
<tr>
<td>Seizure Freq./Month</td>
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<td>82.22</td>
<td>11.52</td>
</tr>
<tr>
<td>VIQ</td>
<td>92.52</td>
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<tr>
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<td>92.50</td>
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<tr>
<td>Handedness (% RH)</td>
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<td></td>
<td>30 (47%)</td>
</tr>
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<td>Gender (% male)</td>
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Table 4

MRI Results of Study Sample

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<tr>
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<td>Right Hippocampal Atrophy &amp;</td>
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<td>0</td>
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<td>Right Mesial Temporal Sclerosis</td>
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<tr>
<td>Right Hippocampal Atrophy,</td>
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<tr>
<td>Increased Left Temporal Horn</td>
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<tr>
<td></td>
<td>44</td>
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*Note. LT = Left Temporal Patients, RT = Right Temporal Patients*
Table 5

T-Test Analyses of Neuropsychological Test Measure Z-Scores as a Function of Left Seizure Focus Group

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<tr>
<th>Measure</th>
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<th>t</th>
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</thead>
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<td>COWA</td>
<td>-1.55</td>
<td>1.22</td>
<td>43</td>
<td>-8.41***</td>
</tr>
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<td>Animal Naming</td>
<td>-1.15</td>
<td>0.98</td>
<td>43</td>
<td>-7.72***</td>
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<td>Digit Span Backwards</td>
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<td>1.74</td>
<td>42</td>
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<td>-1.00***v</td>
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<td>42</td>
<td>0.16v</td>
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<td>2.82</td>
<td>35</td>
<td>4.30v</td>
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<td>3.26</td>
<td>20</td>
<td>5.30***</td>
</tr>
<tr>
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<td>3.96</td>
<td>18</td>
<td>4.26v</td>
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<td>0.92</td>
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<td>43</td>
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<tr>
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<td>2.91**</td>
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</table>

*Note.* DH = Dominant hand; NDH = Non-dominant hand. ð Non-parametric tests used.
†p<.10  *p<.05  **p<.01  ***p<.001
Table 6

Differences Between Pre-Surgical Neuropsychological Test Scores as a Function of Seizure Focus Group

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<td>12.81</td>
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Note. Left Temporal and Right Temporal = Seizure Focus Groups
†= p<.10  *p<.05  **p<.01
Table 7

Analysis of Covariance of Presurgical Test Measures as a Function of Seizure Focus with Duration of Epilepsy, Seizure Outcome, Education, and Age as Covariates

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†p<.10.  *p<.05.  **p<.01.
Table 8

Pre- and Postsurgical Scores as a Function of Seizure Outcome

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<td></td>
<td>Good M/SD</td>
<td>Poor M/SD</td>
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<tr>
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<td>49.63/5.98</td>
<td>44.90/9.85</td>
</tr>
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<td>COWA</td>
<td>32.51/10.56</td>
<td>33.11/8.48</td>
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<tr>
<td>Animals</td>
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<td>18.25/4.83</td>
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<td>Aud. Comp.</td>
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<td>10.00/1.85</td>
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<td>WCST-Cat.</td>
<td>4.96/1.58</td>
<td>5.14/1.22</td>
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<tr>
<td>WCST-PE</td>
<td>15.62/11.40</td>
<td>11.14/5.90</td>
</tr>
<tr>
<td>Trails B</td>
<td>73.50/46.21</td>
<td>80.88/32.21</td>
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<td>Pegs (DH)</td>
<td>78.92/16.78</td>
<td>73.83/19.22</td>
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<tr>
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<td>84.83/28.01</td>
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<td>34.00/8.13</td>
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<td>29.25/6.44</td>
</tr>
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<td>8.14/1.68</td>
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<td>46.11/13.36</td>
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<td>58.82/28.45</td>
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<td>46.00/14.71</td>
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<td>CVLT-LD</td>
<td>10.12/3.16</td>
<td>8.56/4.93</td>
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<tr>
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<td>-23.70/-27.93</td>
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Note. Pre-surgical and Post-surgical = Test times; Good and Poor = Seizure outcome
Table 9

Repeated Measures Analysis of Variance of Neuropsychology Test Measures by Seizure Outcome

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<td>11.88**</td>
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<td>0.05</td>
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<tr>
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<td>8.56**</td>
<td>0.01</td>
<td>0.16</td>
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<tr>
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Table 9 (continued)

Repeated Measures Analysis of Variance of Neuropsychology Test Measures by Seizure Outcome

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†p<.10.  *p<.05.  **p<.01.
Table 10

Pre- and Post-surgical Means and Standard Deviations of Neuropsychological Test Measures as a Function of Seizure Focus and Seizure Outcome Groups

<table>
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<tr>
<th>Measure</th>
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<td>LT</td>
<td>RT</td>
<td>LT</td>
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<td>Poor</td>
<td>Good</td>
<td>Poor</td>
<td>Good</td>
<td>Poor</td>
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<td>9.92</td>
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<td>2.86</td>
<td>1.97</td>
<td>2.62</td>
<td>4.95</td>
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</table>

*Note.* LT = Left Temporal Lobe Group, RT = Right Temporal Lobe Group, Good = Good Outcome Group (Seizure-Free), Poor = Poor Outcome Group (Not Seizure-Free)
Table 11

Repeated Measures Analysis of Variance of Neuropsychological Test Measures as a Function of Seizure Focus and Seizure Outcome Status

<table>
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<td>PrePost*Class</td>
<td>1,57</td>
<td>0.500</td>
<td>0.336</td>
<td></td>
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</tr>
<tr>
<td>PrePost<em>SF</em>Class</td>
<td>1,57</td>
<td>0.367</td>
<td>0.246</td>
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<tr>
<td>SF</td>
<td>1,57</td>
<td>0.823</td>
<td>0.051</td>
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<tr>
<td>Class</td>
<td>1,57</td>
<td>28.984</td>
<td>1.794</td>
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<tr>
<td>SF*Class</td>
<td>1,57</td>
<td>5.675</td>
<td>0.351</td>
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<tr>
<td>Picture Completion</td>
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<td></td>
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<tr>
<td>PrePost</td>
<td>1,44</td>
<td>5.676</td>
<td>1.587</td>
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</tr>
<tr>
<td>PrePost*SF</td>
<td>1,44</td>
<td>0.015</td>
<td>0.004</td>
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</tr>
<tr>
<td>PrePost*Class</td>
<td>1,44</td>
<td>0.790</td>
<td>0.201</td>
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<tr>
<td>PrePost<em>SF</em>Class</td>
<td>1,44</td>
<td>2.232</td>
<td>0.624</td>
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</tr>
<tr>
<td>SF</td>
<td>1,44</td>
<td>12.152</td>
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<tr>
<td>Class</td>
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<td>56.609</td>
<td>4.215*</td>
<td>0.09</td>
<td>0.52</td>
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<tr>
<td>SF*Class</td>
<td>1,44</td>
<td>16.413</td>
<td>1.222</td>
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</tr>
</tbody>
</table>

†p<.10, *p<.05, **p<.01
Table 12

Means and Standard Deviations of Predictor Variables as a Function of Seizure Outcome Status

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Seizure Free</th>
<th>Not Seizure Free</th>
<th>df</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNT</td>
<td>.92</td>
<td>.44</td>
<td>.70</td>
<td>.48</td>
</tr>
<tr>
<td>COWA</td>
<td>1.10</td>
<td>.41</td>
<td>1.22</td>
<td>.44</td>
</tr>
<tr>
<td>Animals</td>
<td>.96</td>
<td>.28</td>
<td>.88</td>
<td>.35</td>
</tr>
<tr>
<td>BDAE Comp.</td>
<td>.90</td>
<td>.59</td>
<td>1.13</td>
<td>.64</td>
</tr>
<tr>
<td>WCST-Cat.</td>
<td>1.04</td>
<td>.21</td>
<td>.86</td>
<td>.38</td>
</tr>
<tr>
<td>WCST-P</td>
<td>1.00</td>
<td>.00</td>
<td>1.14</td>
<td>.38</td>
</tr>
<tr>
<td>Trails B</td>
<td>1.05</td>
<td>.37</td>
<td>1.13</td>
<td>.35</td>
</tr>
<tr>
<td>CVLT-TL</td>
<td>0.76</td>
<td>0.59</td>
<td>0.89</td>
<td>0.33</td>
</tr>
<tr>
<td>CVLT-LD</td>
<td>0.69</td>
<td>0.51</td>
<td>0.44</td>
<td>0.53</td>
</tr>
</tbody>
</table>

*Note.* Good outcome group = Seizure Free; Poor seizure outcome group = Not Seizure Free
Table 13

Correlation of Predictor Variables with Discriminant Functions (Function Structure Matrix) and Standardized Discriminant Function Coefficients

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Function 1</th>
<th>Function 2</th>
<th>Function 3</th>
<th>Function 1</th>
<th>Function 2</th>
<th>Function 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVLT- TL</td>
<td>0.723</td>
<td>0.417</td>
<td>-0.228</td>
<td>0.918</td>
<td>0.633</td>
<td>-0.315</td>
</tr>
</tbody>
</table>

*Note. Function 1 = Seizure Focus, Function 2 = Seizure Outcome, Function 3 = Duration of Epilepsy*
Table 14

Z-Scores of Pre- and Postsurgical Test Measures as a Function of Seizure Outcome

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pre-surgical SF</th>
<th>Pre-surgical NSF</th>
<th>Post-Surgical SF</th>
<th>Post-Surgical NSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNT</td>
<td>-4.58</td>
<td>-7.15</td>
<td>-5.92</td>
<td>-10.06</td>
</tr>
<tr>
<td>COWA</td>
<td>-1.56</td>
<td>-1.47</td>
<td>-1.48</td>
<td>-1.14</td>
</tr>
<tr>
<td>Animals</td>
<td>-1.07</td>
<td>-1.19</td>
<td>-1.13</td>
<td>-1.53</td>
</tr>
<tr>
<td>Aud. Comp.</td>
<td>0.22</td>
<td>-0.16</td>
<td>0.04</td>
<td>-0.15</td>
</tr>
<tr>
<td>WCST-Cat.</td>
<td>-0.09</td>
<td>0.03</td>
<td>0.03</td>
<td>-0.27</td>
</tr>
<tr>
<td>WCST-PE</td>
<td>-0.17</td>
<td>-0.54</td>
<td>0.08</td>
<td>0.48</td>
</tr>
<tr>
<td>Trails B</td>
<td>-1.76</td>
<td>-2.30</td>
<td>-1.88</td>
<td>-2.93</td>
</tr>
<tr>
<td>Pegs (DH)</td>
<td>-3.78</td>
<td>-2.92</td>
<td>-1.90</td>
<td>-1.20</td>
</tr>
<tr>
<td>Pegs (ND)</td>
<td>-3.70</td>
<td>-3.87</td>
<td>-2.78</td>
<td>-2.13</td>
</tr>
<tr>
<td>Grip (DH)</td>
<td>0.02</td>
<td>-0.12</td>
<td>-0.07</td>
<td>-0.15</td>
</tr>
<tr>
<td>Grip (ND)</td>
<td>0.32</td>
<td>-0.17</td>
<td>0.08</td>
<td>-0.45</td>
</tr>
<tr>
<td>ROCF Copy</td>
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<td>-0.62</td>
<td>-0.57</td>
<td>-0.69</td>
</tr>
<tr>
<td>Digits Bkwd</td>
<td>0.09</td>
<td>-0.63</td>
<td>0.43</td>
<td>-0.63</td>
</tr>
<tr>
<td>LM-I</td>
<td>-0.69</td>
<td>-0.37</td>
<td>-0.52</td>
<td>-0.95</td>
</tr>
<tr>
<td>VR-I</td>
<td>0.01</td>
<td>-0.47</td>
<td>0.02</td>
<td>-0.02</td>
</tr>
<tr>
<td>CVLT-TL</td>
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<td>-2.52</td>
<td>-1.96</td>
<td>-2.57</td>
</tr>
<tr>
<td>CVLT-LD</td>
<td>-1.77</td>
<td>-2.68</td>
<td>-2.85</td>
<td>-4.43</td>
</tr>
<tr>
<td>Picture Comp.</td>
<td>-0.11</td>
<td>-1.13</td>
<td>0.05</td>
<td>-0.88</td>
</tr>
<tr>
<td>Picture Arr.</td>
<td>-0.06</td>
<td>-0.44</td>
<td>-0.11</td>
<td>-0.59</td>
</tr>
<tr>
<td>Block Design</td>
<td>0.10</td>
<td>-0.60</td>
<td>0.32</td>
<td>-0.13</td>
</tr>
</tbody>
</table>

*Note.* Pre-surgical and Post-surgical = Test times; Good and Poor = Seizure outcome
APPENDIX D. Figures

Figure 1. One-Sample T-Test Analyses of Neuropsychological Test Measure Z-Scores Comparing Left Temporal Seizure Focus Patients with Controls

= Significant Measures
Figure 2. Pre-surgical Test Scores as a Function of Left and Right Temporal Lobe Seizure Focus
Figure 3. Pre- and Postsurgical Scores of Extra Temporal Measures as a Function of Seizure Outcome Status (Seizure Free vs. Not Seizure Free)
Figure 4. Pre- and Postsurgical Z-Scores of Extratemporal Measures as a Function of Seizure Outcome Status (Seizure Free vs. Not Seizure Free)
Figure 5. Pre and Postsurgical Scores of Right Hemisphere Extra Temporal Measures as a Function of Seizure Outcome Status (Seizure Free vs. Not Seizure Free)
Figure 6. Pre and Postsurgical Scores of Right Hemisphere Extra Temporal Z-Scores as a Function of Seizure Outcome Status (Seizure Free vs. Not Seizure Free)
Figure 7. Pre and Postsurgical Scores of Temporal Lobe Measures as a Function of Seizure Outcome Status (Seizure Free vs. Not Seizure Free)
Figure 8. Pre and Postsurgical Scores of Temporal Lobe Measures as a Function of Seizure Outcome Status (Seizure Free vs. Not Seizure Free)
VITA

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