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SUBTYPES OF MEMORY IMPAIRMENT IN PATIENTS WITH TEMPORAL LOBE EPILEPSY

by

NICOLE C. MICKLEY

Under the Direction of Robin D. Morris

ABSTRACT

Memory impairments are common in individuals with temporal lobe epilepsy (TLE). This is understandable given that temporal lobe brain structures involved in TLE play a central role in encoding memories. It is widely accepted that individuals whose seizure focus is in the left temporal lobe (LTLE) tend to have verbal memory impairments, whereas individuals whose seizure focus is in the right temporal lobe (RTLE) tend to have visuospatial memory impairments. However, evidence of functional subdivisions *within* the left and right temporal lobes in both the animal and human literature suggest that more specific subtypes of memory impairment may exist in TLE based on differences in seizure foci. The aim of this study was to identify more

specific subtypes of memory-impairments in patients with intractable TLE using several measures of memory functioning and cluster analysis. Identification of more specific memory subtypes in TLE could have prognostic significance for patients and contribute to our knowledge about the organization of memory systems of the human brain.

Four memory subtypes were identified in this sample: 1) patients with mild to moderate figural memory deficits; 2) patients with moderate to severe figural memory deficits, mild facial recognition deficits, and mild attention/concentration deficits; 3) patients with severe figural memory deficits and mild verbal episodic memory deficits; and 4) patients with no episodic or semantic memory deficits. Unexpectedly, the subtypes found did not exhibit the expected pattern of verbal memory impairments with left temporal lobe damage/dysfunction or visuospatial memory impairments with right temporal lobe damage/dysfunction. However, consistent with the literature, there was a trend towards some clusters with better verbal memory having higher left hippocampal volumes; and a trend towards one cluster with facial recognition deficits having lower anterior temporal lobe volumes.

Small sample sizes in this study limited the ability to clearly validate many of the cluster differences, particularly differences in brain volumes. Nevertheless, the results of this study support the hypothesis that subtypes of memory impairment *do* exist in patients with TLE. With larger sample sizes, it is plausible that additional subtypes may be found, or the characteristics of the subtypes found may become clearer.

INDEX WORDS: Epilepsy, Neuropsychology, Episodic memory, Semantic memory, Memory, Cluster analysis, Temporal lobe, Hippocampus, Perirhinal cortex, Anterior temporal lobe, MRI

SUBTYPES OF MEMORY IMPAIRMENT IN PATIENTS WITH TEMPORAL LOBE EPILEPSY

by

NICOLE C. MICKLEY

A Dissertation Submitted in Partial Fulfillment of the Requirements of the Degree of

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Georgia State University

2009

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2009

SUBTYPES OF MEMORY IMPAIRMENT IN PATIENTS WITH TEMPORAL LOBE EPILEPSY

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Table of Contents

Acknowledgments v

List of Tables x

List of Figures xi

Introduction 1

Episodic Memory 4

Verbal episodic memory. 7

Visuospatial episodic memory. 10

Semantic Memory 14

Other Factors Associated with Memory Impairment in Epilepsy 18

Purpose of Study 20

Method 23

Sample and Participant Selection 23

Neuropsychological Assessment and Measures 26

California Verbal Learning Test – Second Edition (CVLT-II). 27

Wechsler Memory Scale –Third Edition (WMS-III). 28

Logical Memory. 28

Verbal Paired Associates. 29

Faces. 30

Spatial Span. 30

Taylor Complex Figure. 31

Boston Naming Test. 32

Wechsler Intelligence Scales. 33

Vocabulary. 33

Digit Span. 33

Brain Volume Assessment (for Validation of Clusters) 34

Definition of hippocampal boundaries. 38

Definition of perirhinal cortex boundaries. 39

Definition of anterior temporal lobe boundaries. 39

Statistical Analyses 39

Principal components analysis. 39

Cluster analysis. 41

Assessment of internal and external validity of clusters. 44

Cluster analysis of alternative classification variables. 44

Comparison of cluster analysis and neuropsychological classification. 45

Comparison of cluster analysis and neuroradiological classification. 45

Results 46

Cluster Analysis 46

Selection of optimal cluster size 46

Cluster performance on classification and demographic variables 46

Two-cluster solution. 46

Three-cluster solution. 49

Six-cluster solution. 52

Assessment of Internal and External Validity of Clusters 55

Volumetric Analysis of Clusters 55

Cluster Analysis of Alternative Classification Variables 57

Clinical Classifications Compared to Cluster Assignment 57

Neuropsychological classification of patients. 57

Volumetric analysis of neuropsychologically classified groups. 61

Neuroradiological classification of patients. 62

Volumetric analysis of neuroradiologically classified patients. 66

Discussion 67

Two-cluster solution 68

Three-cluster solution 69

Six-cluster solution 71

References 83

Appendix A: Volumetric Analysis of Clusters (MRI Scans Divided into Two Groups Based on Slice Thickness) 98

"Slicegroup 1" (1mm and 2mm MRI Scans Only) 98

"Slicegroup 2" (1.25 – 1.5mm MRI Scans Only) 99

Appendix B: Bonferroni Post-Hoc Comparisons: Significant Group Differences on Classification Variables for the Three- Cluster Solution 100

Appendix C: Bonferroni Post-Hoc Comparisons: Significant Group Differences on Classification Variables for the Six-Cluster Solution 101

Appendix D: Bonferroni Post-Hoc Comparisons: Significant IQ Differences for the Six-Cluster Solution 102

Appendix E: Volumetric Analysis of Groups Classified Based on Neuropsychological Test Performance (MRI Scans Divided Into Two Groups Based on Slice Thickness) 103

"Slicegroup 1" (1mm and 2mm MRI Scans Only) 103

"Slicegroup 2" (1.25 – 1.5mm MRI Scans Only) 103

Appendix F: Volumetric Analysis of Groups Classified by EEG/Neuroimaging (MRI Scans Divided into Two Groups Based on Slice Thickness) 105

“Slicegroup 1” (1mm and 2mm MRI Scans Only) 105

“Slicegroup 2” (1.25 – 1.5mm MRI Scans Only) 105

List of Tables

Table 1 Demographic and Clinical Characteristics of Participants M (SD) 23

Table 2 Epilepsy Syndrome and Areas of Identified Brain Damage/Dysfunction for Final Sample 25

Table 3 Sample Means and Standard Deviations on Principal Components Analysis Variables 27

Table 4 Intra-Rater Reliabilities for the Six Regions of Interest (ROIs) 37

Table 5 Highest Loading Measures on the Five PCA Components 41

Table 6 Means of Two Clusters on Neuropsychological Tests M (SD) 47

Table 7 Two Cluster Demographic and Seizure Characteristics M (SD) 49

Table 8 Means of Three Clusters on Neuropsychological Tests M (SD) 50

Table 9 Significant Differences on Classification Variables for 3-Cluster Solution 51

Table 10 Three Cluster Demographic and Seizure Characteristics M (SD) 52

Table 11 Comparison of Six Clusters Performance on Neuropsychological Tests M (SD) 53

Table 12 Chi-Square Contingency Table: 6-Clusters by Level of Impairment 54

Table 13 Six Cluster Demographic and Seizure Characteristics M (SD) 55

Table 14 Comparison of Ward’s Method 2-Cluster Assignment With Neuropsychological Classification 58

Table 15 Comparison of Ward's Method 3-Cluster Assignment With Neuropsychological Classification 59

Table 16 Comparison of Ward's Method 6-Cluster Assignment With Neuropsychological Classification 60

Table 17 Z-Scores on Classification Variables for Neuropsychologically Classified Groups M (SD) 60

Table 18 Comparison of Ward's Method 2-Cluster Assignment With Neuroradiological Classification 63

Table 19 Comparison of Ward's Method 3-Cluster Assignment With Neuroradiological Classification 64

Table 20 Comparison of Ward's Method 6-cluster Assignment With Neuroradiological Classification 64

Table 21 Z-Scores on Classification Variables for Groups Classified by EEG/Imaging M (SD) 65

List of Figures

Figure 1. Performance of two clusters on classification variables. 48

Figure 2. Performance of three clusters on classification variables. 50

Figure 3. Performance of six clusters on classification variables. 53

The term “epilepsy” refers to a group of neurological disorders whose central feature is recurrent unprovoked seizures (i.e., sudden, transient disturbances of electrical activity in the brain). Epilepsy can be classified into two broad categories: 1) generalized epilepsy, in which seizures typically begin simultaneously in both cerebral hemispheres; and 2) partial epilepsy, in which seizures originate in one or more localized foci. The most common type of partial epilepsy is temporal lobe epilepsy (TLE), which comprises approximately 40% of adult epilepsy cases (Alessio et al., 2004).

Impairments in cognitive functioning are relatively common in epilepsy patients. In fact, these deficits are often more debilitating than the seizures themselves (Rausch & Langfitt, 1997). The nature of these deficits varies depending upon which areas of the brain are impacted by the disorder. In individuals with TLE, mild to moderate deficits have been reported in intelligence, academic achievement, language functions, visuospatial functions (Hermann, Seidenberg, Schoenfeld, & Davies, 1997), executive functions, and motor speed (Oyegbile et al., 2004); however, memory impairments are particularly prominent. This is because the temporal lobe brain structures involved in TLE play a central role in consolidating information into memory.

The term “memory” actually refers to a collection of mental abilities that depend on several systems in the brain. Four hypothesized memory systems that have been suggested are: 1) episodic memory; 2) semantic memory; 3) short-term memory; and 4) procedural memory. Episodic memory refers to knowledge about specific, personally-experienced events. Some examples include remembering a conversation at a party, remembering where one’s car is parked, or remembering a list of items to buy at the

grocery store. Semantic memory refers to general factual knowledge, such as the name of the first president of the United States, the color of grass, or the meaning of the word “bird.” Short-term or immediate memory refers to a limited-capacity system that temporarily holds information in awareness while it is processed in some way. For example, one might rehearse a phone number in short-term memory until it can be written down. Finally, procedural memory refers to a system for storing behavioral algorithms, such as the steps involved in riding a bicycle, or knitting a sweater.

In patients with TLE, procedural memory and short-term memory are typically intact (Squire, Stark, & Clark, 2004), whereas episodic memory is frequently impaired. This is because encoding of episodic memories appears to depend particularly on brain structures in the right and left medial temporal lobes. (These structures will be discussed in more detail shortly.) Deficits in semantic memory have also been reported in patients with TLE (e.g., Giovagnoli, Erbetta, Villani, & Avanzini, 2005; Tröster et al., 1995), which is not surprising given that the semantic memory system also depends on temporal lobe structures. However, the vast majority of research in TLE is focused on episodic memory, with a secondary focus on semantic memory. Whether there are subtypes of TLE based on their pattern of memory deficits is the focus of this study.

It is important to add here that, although encoding of episodic and semantic memories depends particularly upon the temporal lobes, other structures outside the temporal lobes also contribute to the formation of episodic memories (e.g., midline diencephalic structures, and the frontal lobes; Johnson, Saykin, Flashman, McAllister, & Sparling, 2001). Some of these structures, such as the mamillary bodies, are believed to play a direct role in the encoding of memories (Martin et al., 1998). Other areas of the

brain are thought to play more of a supporting role. For example, the frontal lobes may contribute to an individual's performance on memory tasks through their impact on attention and organizational strategies. It is difficult, if not impossible, to parcel out the impact of these structures on memory performance. As a result, there are no pure measures of memory. So-called episodic memory tasks are labeled thus because they are believed to tax the episodic memory system more heavily than other cognitive abilities; however, these tasks most certainly draw on other cognitive abilities as well.

The remainder of this introduction is divided into three sections. Section one covers episodic memory. It begins with a general overview of the structure of the episodic memory system. This is followed by more detailed information regarding verbal episodic memory, including a description of tasks used to assess verbal episodic memory, a description of brain structures important for verbal episodic memory formation, and a brief review of the literature on verbal episodic memory in patients with TLE. Next, more detailed information on visuospatial episodic memory is provided, including a description of tasks used to assess visuospatial memory, a description of brain structures important for different aspects of visuospatial memory, and a brief review of the literature on visuospatial episodic memory in patients with TLE.

Section two of this introduction covers semantic memory. It begins with a description of tasks used to assess semantic memory. This is followed by a description of the areas of the brain thought to be most important for semantic memory formation, and a brief review of the literature on semantic memory in patients with TLE.

Section three of this introduction covers other factors which might impact memory performance in patients with epilepsy. These factors include seizure variables

(age at onset of seizures, and duration of seizures) and demographic variables (educational level, and sex). The introduction concludes with the aims and hypotheses of the present study.

Episodic Memory

As was noted earlier, the episodic memory system depends particularly upon structures within the medial temporal lobes. These structures include the hippocampal formation (including the hippocampus proper, the dentate gyrus, and the subicular complex), and portions of the parahippocampal gyrus (including the entorhinal, perirhinal, and parahippocampal cortices; Squire et al., 2004). The left and right hippocampal regions are of particular interest to epilepsy researchers. This is because these structures appear to play a prominent role in seizure propagation, and surgical removal of a malfunctioning hippocampus renders many medically-refractory patients seizure-free (Schwarcz & Witter, 2002). However, a growing body of research has also been published on the role of the perihippocampal cortical regions (such as the perirhinal cortex and entorhinal cortex) in episodic memory (O'Brien, Bowden, Bardenhagen & Cook, 2003; Weintrob, Saling, Berkovic, Berlangieri & Reutens, 2002). These structures lie adjacent to the hippocampi within the mesial temporal lobes and are connected to the hippocampus (directly in the case of the entorhinal cortex, and indirectly in the case of the perirhinal cortex via relays in the entorhinal cortex; O'Brien et al., 2003).

Numerous studies have been published showing a relationship between neuronal volume of these brain structures and memory performance. Many of these studies have been conducted with TLE patients, approximately 40-70% of whom exhibit unilateral or

bilateral reduction in hippocampal neuronal volume compared to normal controls (Reminger et al., 2004). This is a condition known as hippocampal sclerosis (HS). In some TLE patients, similar patterns of neuronal loss have also been reported in the perirhinal cortex (PrC) and the entorhinal cortex (EC). Thus, the term “mesial temporal sclerosis” (MTS) is sometimes used instead of hippocampal sclerosis. In patients with TLE, greater hippocampal sclerosis is associated with lower preoperative memory (Alessio et al., 2004). In addition, it has been found that patients with greater left HS are less likely to suffer a verbal memory decline following left temporal lobectomy (Hermann, Wyler, Somes, Berry, & Dohan, 1992; Trenerry, Westerveld, & Meador, 1995). Hippocampal sclerosis has also been found to be related to intellectual function and language (Alessio et al., 2004; Trenerry, Westerveld, & Meador, 1995).

It is generally accepted that left temporal structures are more important in memory for verbal information, whereas right temporal structures are more involved in memory for visuospatial information (Barr, 1997; Dige & Wik, 2001; Gleissner, Helmstaedter, & Elger, 1998; Glogau, Ellgring, Elger & Helmstaedter, 2004). Milner (1966) was one of the first researchers to describe the presence of material-specific deficits in patients following unilateral temporal lobectomy. Since that important early study, many researchers have reported deficits in verbal memory performance in epilepsy patients whose seizure focus is in the left temporal lobe (LTLE; Alessio et al., 2004; Baxendale, 1997; Lacritz, et al., 2004) and deficits in visuospatial memory in patients whose seizure focus is in the right temporal lobe (RTLE; Barr, 1997; Dige & Wik, 2001). The link between left temporal lobe structures and verbal abilities, and right

temporal lobe structures and visuospatial abilities, has been found not only in epilepsy patients, but also in patients with probable Alzheimer's disease (de Toledo-Morrell et al., 2000).

The association between right temporal structures and visuospatial memory is not as robust as the association between left temporal structures and verbal memory (Alessio et al., 2004; Baños et al., 2004; Barr, 1997). One explanation for this finding is that visuospatial memory may have more widespread or bilateral representation in the brain (Alessio et al., 2004). An alternative hypothesis is that individuals may be particularly likely to encode some visual information verbally during visuospatial memory tasks. For example, when asked to memorize a figure, a person might think, "It is a rectangle divided into four equal parts with a triangle attached to the right side." In support of this hypothesis, visual deficits are more easily demonstrated in children with RTLE, presumably because they have not yet learned to use a verbal encoding strategy (Jambaqué, Dellatolas, Dulac, Ponsot, Signoret, 1993; Nolan et al., 2004).

In summary, the episodic memory system appears to depend particularly on several structures within the medial temporal lobes, including the hippocampal formation and portions of the parahippocampal gyrus (e.g., the perirhinal cortex). The hippocampus has been a primary focus in published research on episodic memory impairment in TLE because this structure appears to play a central role in seizure propagation. However, there is evidence that different temporal lobe structures are important for different aspects of episodic memory. Rather than examining the individual contributions these structures make to episodic memory, most TLE researchers have focused on differences in memory performance between patients with

left temporal lobe damage or dysfunction versus memory performance in patients with right temporal lobe damage or dysfunction. It is generally accepted that left temporal lobe structures are more important for verbal memory impairments, whereas right temporal lobe structures are more important for visuospatial memory. However, the literature demonstrating verbal memory impairments in patients with left hemisphere damage or dysfunction is more robust.

Verbal episodic memory. Verbal episodic memory is often assessed by reading a short story or a list of words to the patient who is then asked to recall as much of the information as he or she can remember. Recall trials are often administered immediately after the to-be-remembered information is presented and again after a delay. Other data that are often collected include the percent of information retained between immediate and delayed recall trials, and learning efficiency (ability to benefit from repetition). Another common verbal episodic memory task assesses memory for word pairs. In this task, a list of unrelated word pairs is read to the patient. The patient is then provided with the first word in each pair and is asked to recall the second word. Recall trials are administered immediately after the to-be-remembered information is presented and again after a delay.

A small number of studies have been published demonstrating involvement of the perirhinal cortex in verbal episodic memory. For example, Weintrob, Saling, Berkovic, & Reutens (2007) reported impaired memory for word pairs in a small sample of patients who underwent left perirhinal cortex resection with sparing of the hippocampus. Similarly, Alessio et al. (2006) observed that asymmetry between left and right perirhinal cortex volumes predicted performance on measures of verbal

memory in a sample of TLE patients. (As noted earlier, decreased neuronal volume is an index of sclerosis.) However, the number of studies published on the role of the perirhinal cortex in verbal episodic memory is limited.

In contrast, numerous studies have demonstrated a relationship between performance on verbal episodic memory tasks and hippocampal volume (Bell, Hermann, & Seidenberg, 2004; Griffith, Pyzalski, Seidenberg, and Hermann, 2004; Martin et al., 1999). Most often, left hippocampal volume is associated with performance on verbal memory tasks. For example, in patients with both left and right TLE, Bell et al. found that left but not right hippocampal volume was associated with delayed recall of prose, immediate and delayed recall of word pairs, and immediate and delayed verbal memory indices on the Wechsler Memory Scale –III (WMS-III).

Other studies have shown that right, left, and bilateral hippocampal volumes are all significant predictors of verbal episodic memory performance. For example, Griffith et al. (2004) found that left, right, and bilateral hippocampal volumes all predicted percent retention scores on a measure of memory for word pairs (WMS-III Verbal Paired Associates Percent Retention).

Still other studies have only found a relationship between verbal episodic memory performance and bilateral hippocampal lobe volumes. For example, Griffith et al. (2004) found that bilateral, but not unilateral, hippocampal volumes predicted percent retention scores on a task of memory for stories (WMS-III Logical Memory Percent Retention score); and Reminger et al. (2004) found that bilateral, but not unilateral, hippocampal volume significantly predicted delayed recall of stories (Logical Memory II). Similarly, Sawrie, Martin, Gilliam et al. (2001) found that patients with LTLE scored

significantly lower than patients with RTLE on the WMS-III Logical Memory percent retention only when bilateral hippocampal atrophy was present. LTLE patients with normal hippocampal volumes or unilateral hippocampal atrophy on MRI performed similarly to patients with RTLE.

Despite the large body of research demonstrating a relationship between hippocampal volume and verbal episodic memory, some studies have not found a relationship between the two. O'Brien et al. (2003) found that only the *difference* between left hippocampal and left perirhinal cortex volumes significantly predicted verbal memory scores (the WMS-III composite Verbal Memory Index score and a Logical Memory composite score) in patients with TLE. Left or right perirhinal or hippocampal volumes alone were *not* significant predictors. Similarly, Weintrob et al. (2002) found that resting glucose uptake in the left perirhinal cortex was associated with performance on a task of memory for word-pairs, whereas hippocampal volume did not explain any additional variance in memory scores.

In summary, many (but not all) studies have demonstrated a relationship between verbal episodic memory performance and hippocampal volume. Though most published studies have demonstrated a relationship between memory performance and left hippocampal volume, relationships between right and bilateral hippocampal volumes and memory performance have also been reported in the literature. Much less research has been published on the role of other temporal lobe structures in verbal episodic memory; however, there is some evidence that the left perirhinal cortex is also involved in verbal episodic memory. Much more is known about the role of the perirhinal cortex

and other temporal lobe structures in visuospatial memory performance, thanks primarily to the animal research literature. These studies will be reviewed briefly below.

Visuospatial episodic memory. Three different types of tasks are commonly used to assess visuospatial memory: 1) figural memory tasks, 2) facial recognition tasks, and 3) spatial memory tasks. Figural memory is assessed by showing a patient simple shapes or complex figures, and then asking him or her to draw the figure(s) from memory. Facial recognition is frequently assessed by showing a patient a series of photographs of unfamiliar faces, and then asking him/her to discriminate between novel and previously presented faces. Spatial memory has been assessed using several different paradigms including: 1) maze learning tasks, 2) memory for block sequences, and 3) virtual reality navigation tasks.

Much of our knowledge about the brain structures important for visuospatial memory comes from the animal research literature. There is evidence from these studies that there are functional subdivisions within the medial temporal lobes, such that the hippocampus is particularly important in spatial memory and associative recognition memory (e.g., recognizing an object and where it was seen before; Parkinson, Murray, & Mishkin, 1988), whereas the perirhinal cortex is important in object recognition memory (e.g., simply recognizing an object as familiar, but not recollecting information about where or when it had been previously presented; Meunier, Bachevalier & Mishkin, 1997; Brown & Aggleton, 2001).

For example, in rats, hippocampal lesions (Abe, Ishida, Nonaka, & Iwasaki, 2009; Stubley-Weatherly, Harding, & Wright, 1996) and kindling of the dorsal hippocampus (Hannesson et al., 2005) have been shown to disrupt spatial memory,

whereas perirhinal lesions (Abe et al., 2009) and kindling of the perirhinal cortex in rats have been shown to impair object recognition memory (Hannesson et al., 2005). Winters, Forwood, Cowell, Saksida & Bussey (2004) found that complete excitotoxic lesions of the hippocampus in rats resulted in spatial memory impairment with preserved object recognition memory, whereas excitotoxic lesions of the perirhinal cortex resulted in object recognition memory deficits with preserved spatial memory. Congruently, in rhesus monkeys, lesions restricted to the perirhinal cortex have been found to result in severe impairment in visual recognition memory (Meunier, Bachevalier, Mishkin, & Murray, 1993).

Consistent with the animal research literature, both Ross & Slotnick (2008) and Staresina & Davachi (2008) have found fMRI activation of the hippocampus in human subjects during tasks of associative recognition memory, whereas perirhinal cortex activation was observed during nonassociative, item-memory tasks or during memory tasks in which association was limited to item-related features (such as the color of the item).

With respect to face recognition, there is evidence that these tasks rely on still different temporal lobe structures than spatial memory tasks (Barr 1997). This evidence originates from research in visual cognition and the neurosciences which has identified a ventral system for encoding and storing properties of objects, such as shape color and texture (the “what” system), and a dorsal system for processing spatial properties, such as orientation and location (the “where” system; Ungerleider & Mishkin, 1982).

In humans, analogous systems have been identified. For example, a ventral memory system, which includes the fusiform gyrus and anterior temporal pole, appears

to play a role in facial recognition. Damasio, Tranel, & Damasio (1990) describe a disorder caused by bilateral lesions to the temporal pole ("amnestic associative prosopagnosia") in which perception of faces is preserved, but recognition of faces is impaired. Bengner, Siemonsen, Stodiek, & Fiehler (2008) found that combined T2 values for the hippocampus and fusiform gyrus were significantly correlated with immediate recognition of faces in a sample of epilepsy patients. In addition, lower right than left T2 relaxation times in the fusiform gyrus was significantly related to better face recognition. Dissociation of the "what" and "where" systems in individuals with TLE has been reported by Barr (1997), who found impaired facial recognition, but preserved spatial abilities in a group of RTLE patients compared to LTLE patients. In addition, Hermann, Seidenberg, Wyler, & Haltiner (1993) reported dissociation of these two systems in patients following temporal lobectomy. Specifically, facial matching abilities mediated by the ventral system were reportedly compromised by right anterior temporal lobectomy, whereas dorsal system functions were spared.

Most studies in the human epilepsy literature; however, are focused on differences between patients with LTLE and RTLE on measures of visuospatial memory rather than on the contribution of specific temporal lobe brain structures to visuospatial memory. As was noted earlier, it is widely accepted that patients with right temporal lobe dysfunction perform worse on tasks of visuospatial memory than patients with left temporal lobe dysfunction. Many studies have been published in support of this hypothesis. For example, Bengner et al., (2008) and Barr (1997) found that RTLE patients performed significantly worse on a facial recognition memory test (the Denman Facial Recognition Test) than patients with LTLE. Jokeit et al (1997) found that patients

with RTLE performed significantly worse than LTLE patients on delayed free recall of a complex figure. Smith and Milner (1981) and Petrides (1985) have reported spatial learning deficits in right temporal lobectomy patients.

Many studies; however, have demonstrated that patients with TLE are impaired on visuospatial tasks, regardless of the side of their seizure focus. For example, Glikmann-Johnston et al. (2008) found that both right and left TLE patients performed significantly worse than controls on three different spatial memory tasks assessed via a virtual-reality paradigm. However, there were no differences in performance between patients with a left temporal seizure focus versus patients with a right temporal seizure focus. Glogau et al. (2004) and Reminger et al. (2004) found that adults with RTLE and LTLE performed significantly worse than controls on a task of face memory. On measures of figural memory, Lacritz et al. (2004) found that adults with both left and right TLE performed in the borderline to low average range, and significantly worse than a standardization sample in both immediate and delayed free recall. Similarly, McConley et al. (2008), and Kneebone, Lee, Wade and Loring (2007) found no significant differences between LTLE and RTLE patients on a task of figural memory. What is most interesting about these last two studies; however, is that they found stronger associations between *left* temporal lobe function and performance on this task. Kneebone and colleagues speculated that this may be due to the verbalizability of many of the test's components. Finally, it should be noted that some studies report no relationship between right TLE and visuospatial memory deficits (Alessio et al., 2004; Chelune, Naugle, Luder, & Awad, 1991; Hermann et al., 1995; Naugle et al., 1994).

In summary, there is evidence that different temporal lobe structures contribute to different aspects of visuospatial memory. Much of this evidence comes from the animal research literature. The results of these studies suggest that: 1) the hippocampus plays an important role in spatial memory and associative recognition memory, 2) the perirhinal cortex plays an important role in object recognition memory, and 3) the anterior temporal lobes and the fusiform gyri play an important role in facial recognition. Similar findings have been reported in the human literature; however, the results are less clear. This is partly because the majority of research is focused on differences between patients with damage or dysfunction in the right versus left temporal lobes. Many studies have demonstrated that right temporal lobe structures are more important for visuospatial information; however, a significant body of research has demonstrated that patients with both left and right temporal lobe damage or dysfunction perform poorly on visuospatial memory tasks. These results may be due to more widespread representation of visuospatial memory in the brain, functional reorganization of the brain, or verbal encoding of some aspects of visuospatial tasks.

Semantic Memory

It has been hypothesized that the semantic memory system is a primitive memory system from which the episodic memory system evolved (Tulving, 1972). Both memory systems depend particularly on structures within the temporal lobes. However, there is some controversy as to whether certain mesial temporal lobe structures are more important for semantic versus episodic memory. Vargha-Khadem et al. (1997) and Mishkin, Vargha-Khadem, and Gadian (1998) propose that encoding of semantic memory depends primarily upon the entorhinal and perirhinal cortices, whereas

encoding of episodic memory depends primarily on the hippocampus. In support of their hypothesis are recent case reports of patients who appear to have intact semantic memory after sustaining early limited hippocampal damage (Baddeley, Vargha-Khadem, & Mishkin, 2001; Vargha-Khadem et al., 1997). These case studies led Tulving and Markowitsch (1998) to propose a model of memory in which: (1) encoding of episodic memories depends upon the semantic memory system, but not vice-versa; and (2) that retrieval of semantic memories or episodic memories can be supported by either of the two systems or both of them. The functional subdivisions of the hippocampus and perirhinal cortex proposed by Vargha-Khadem et al. is consistent with the animal research literature which has demonstrated a greater role of the perirhinal cortex in simple recognition memory tasks (recognizing an object that has been presented before) and a greater role of the hippocampus in associative memory tasks that require remembering a stimulus *and* the context in which it was presented (e.g., where it was presented and/or with what other stimuli).

An alternative model of semantic memory has been proposed by Squire and Zola (1998). In their “sole route of entry” model of memory, they propose that semantic memories are merely episodic memories that are subject to repetition or habit formation (Knowlton & Squire, 1995). Thus, they propose that encoding of episodic and semantic memory depends similarly on medial temporal lobe structures. In support of this model, they argue that amnestic patients invariably exhibit both impairment in episodic memory *and* a failure to update semantic memory. Furthermore, they argue that in case reports such as those published by Vargha-Khadem et al. (1997) patients *did* exhibit semantic memory impairments in addition to episodic

memory impairments; and they maintain that the researchers were unable to prove that these semantic memory impairments were, in fact, milder than the accompanying episodic memory impairments. Even if it could be proven that semantic memory was less impaired than episodic memory impairments in these patients, Squire et al. (2004) hypothesized that this might be explained by functional reorganization that occurred due to the early age at which this patients sustained hippocampal damage. In other words, these patients may have developed an atypical method of acquiring semantic memories. Thus, it remains to be determined whether the perirhinal cortex and hippocampus are specialized for encoding semantic and episodic memories, respectively.

The literature on semantic dementia, a disease in which semantic memory is impaired while aspects of episodic memory are preserved, suggests that other temporal lobe regions are important for semantic memory. In particular, there has been much interest in the role of the temporal pole in semantic memory. Patients with semantic dementia have been found to exhibit neuronal loss in the temporal pole (Galton et al., 2001; Mummery et al., 1999). Left temporal pole volume (and inferior and middle temporal gyri volume), but not medial temporal lobe volumes, were found to correlate with semantic naming and category fluency tasks in patients with semantic dementia and in patients with Alzheimer's disease (Galton et al., 2001). Similarly, in a group of patients with various forms of temporal lobe damage, Schmolck, Kensinger, Corkin & Squire (2002) found that impairment on a battery of semantic knowledge tasks was related to the extent of damage to anterolateral temporal cortex and not medial temporal structures.

In the epilepsy literature, several studies have been published demonstrating semantic memory deficits in patients with TLE. Messas, Mansur, and Castro (2008) found that both right and left TLE patients performed significantly worse than controls on measures of confrontation naming of nouns, word-picture matching, and word list generation. In addition, patients with left TLE showed deficits on measures of word definition compared to both controls and right TLE patients. Tröster et al. (1995) reported that semantic verbal fluency was impaired in both right and left TLE patients relative to controls, but patients with LTLE exhibited the greatest impairment. Finally, Giovagnoli et al. (2005) reported that LTLE patients performed significantly worse than both RTLE patients and controls on several measures of semantic memory. In the Giovagnoli study, the type of semantic deficits seemed to vary based on foci location. Specifically, LTLE patients with lateral temporal lobe foci were impaired on a picture naming task, whereas patients with mesial temporal lobe foci were impaired on a task requiring semantic decision making.

In summary, there is some controversy as to whether certain mesial temporal lobe structures are more important for semantic versus episodic memory. Some researchers have argued that encoding of semantic memory depends primarily upon the entorhinal and perirhinal cortices, whereas encoding of episodic memory depends primarily on the hippocampus (Vargha-Khadem et al., 1997; Mishkin et al., 1998). Others have argued that encoding of episodic and semantic memory depends similarly on medial temporal lobe structures (Squire & Zola, 1998). There is also evidence, particularly in the semantic dementia literature, that the left temporal pole is important in semantic memory. In the epilepsy literature, most published studies have focused on

the role of a left versus right temporal lobe seizure focus in semantic memory. In general, these studies have demonstrated semantic memory impairments in patients with both right and left temporal lobe seizure foci. However, deficits in patients with left seizure foci appear to be more severe.

Other Factors Associated with Memory Impairment in Epilepsy

In addition to differences in seizure foci, other factors that have been found to impact memory functioning in TLE patients include their age at seizure onset, frequency of seizures, duration of epilepsy (time since diagnosis), and antiepileptic drug (AED) polypharmacy (Alessio et al., 2004). Earlier seizure onset has been associated with greater and more diffuse cognitive impairment (Dodrill & Matthews, 1992). For example, Lespinet, Bresson, N'Kaoua, Rougier, and Claverie (2002) found that individuals with early TLE onset (0-5 years) exhibited significant global cognitive deficits including deficits in both verbal and visuospatial memory. In contrast, individuals with late onset TLE exhibited more circumscribed deficits. Specifically, late onset RTLE adults tended to be impaired on visuospatial memory tasks, whereas late onset LTLE adults were primarily impaired on verbal memory tasks.

Longer history of seizures has also been associated with poorer prognosis. For example, in a sample of 96 TLE patients, Oyegbile and colleagues (2004) found that a longer history of seizures was associated with impaired performance on measures of intelligence, memory, language, visuoperceptual, and motor tasks. This finding was significant even when controlling for number of anti-epileptic drugs, history of status epilepticus, and number of generalized tonic-clonic seizures. Similarly, in a selective

literature review, Dodrill (2004) concluded that losses in mental abilities occur over time in patients with uncontrolled seizures.

Educational level has been another important variable when considering the impact of TLE on cognitive functioning. Oyegbile et al. (2004) found that the relationship between duration of epilepsy and cognitive impairment was attenuated in patients with greater than 12 years of education. Similarly, Lespinet et al. (2002) found that educational level was a significant predictor of verbal and visuospatial memory scores in a group of 56 unilateral temporal lobe epilepsy patients.

Even a patient's sex has been reported to interact with memory functioning in TLE. Results of several studies suggest that verbal memory is less lateralized in women than in men. For example, Trenerry, Jack, Cascino, Sharbrough, and Ivnik (1995) found that both left and right hippocampal volume significantly predicted verbal memory performance in women, but not in men. Helmstaedter, Kurthen and Elger (1999) found that LTLE men exhibited the expected pattern of impaired verbal memory performance, whereas LTLE women exhibited greater impairment in visuospatial memory. Geckler, Chelune, Trenerry and Ivnik (1993) found that women performed significantly better than men on measures of verbal memory following left temporal lobectomy.

In summary, variables other than seizure foci that have been found to impact memory performance in patients with TLE include age at onset of seizures, duration of seizure disorder, educational level, and sex. Earlier seizure onset has been associated with greater and more diffuse cognitive impairment, whereas later onset of seizures has been associated with more circumscribed deficits. A longer history of seizures (time

since diagnosis) and fewer years of education have both been associated with poorer memory performance. And, finally, sex has been associated with differences in verbal memory lateralization (i.e., verbal memory may have more bilateral representation in women than in men).

Purpose of Study

Based on this review of the literature, it is reasonable to expect that subtypes of memory impairment exist in TLE patients based on differences in their seizure foci and the other variables which have been associated with memory performance described above. However, the past failure to identify such subtypes might be due to either memory measures that lack discriminative validity (McConley et al., 2008; Loring et al., 2008; Raspall et al., 2005; Wilde et al., 2001), or to an invalid classification system. Classification has been identified as “a fundamental problem area” in neuropsychology because how patients are classified impacts their treatment and prognosis, but also validates our theoretical models regarding brain function (Morris & Fletcher, 1988, p. 641). In epilepsy research, the common practice of clinically classifying patients based on temporal or extratemporal seizure focus, or even left versus right temporal seizure focus, may not be the best classification system for understanding their differences on measures of memory functioning, deciding on treatments, or predicting prognosis. For example, one recent study investigated the validity of separate auditory delayed and immediate indices on the Wechsler Memory Scale –III (WMS-III) in a sample of 88 TLE patients who were classified based on right or left seizure focus (Bell et al., 2004). The researchers concluded that most patients did not exhibit a significant discrepancy between the delayed and immediate indices. Thus, they concluded that it would be

appropriate to combine these indices in TLE patients. However, at the same time it is significant to note that 13% of the patients in that study *did* exhibit a significant discrepancy between these scores (obtaining a delayed index score >13 point lower than their immediate index) and might have represented a specific subtype of TLE. However, the existence of this subtype would have been concealed by more traditional group level comparisons of memory performance (e.g., LTLE vs. RTLE). One potential problem with missing such subtypes is that these patients may have different treatment prognoses. In addition, the identification of reliable subtypes of memory impairment in TLE could increase our knowledge about the more specific organization of memory systems of the human brain.

With this in mind, the aim of the present study was to use a quantitative classification method, cluster analysis, to identify subtypes of memory-impairments in patients with TLE. To the author's knowledge, only one other study has used such an approach to identify different cognitive phenotypes in patients with TLE. In that study, Hermann, Seidenberg, Lee, Chan, and Rutecki (2007) reported obtaining three cognitive phenotypes in a sample of patients with TLE. Though these researchers compared patients' performance on a number of different cognitive variables in addition to memory (e.g., executive functioning, processing speed, and language), the three groups obtained by these researchers were described as having mild, moderate, and severe memory impairment.

In the present study, it was hypothesized that five subtypes of TLE would be identified. Subtype 1 was expected to display verbal episodic memory deficits, which may be related to restricted lesions of the left hippocampus and later seizure onset.

Subtype 2 was expected to display both verbal episodic and semantic memory deficits due to more widespread left temporal lesions including perirhinal and anterior temporal pole regions. Subtype 3 was expected to show deficits in figural episodic memory and spatial memory, which may be due to restricted right hippocampal lesions and later seizure onset. Subtype 4 was expected to show global visuospatial memory deficits (figural episodic, spatial, and face recognition), which may be related to more widespread right temporal involvement including the hippocampus, perirhinal cortex, and anterior temporal pole. Finally, subtype 5 was expected to show global verbal and visuospatial memory deficits, which may be related to earlier seizure-onset and bilateral temporal lobe lesions.

In addition to the above subtypes, it was expected that patients with seizure onset at an earlier age would demonstrate more global impairment (verbal plus visuospatial deficits) than patients with later seizure onset. It was also expected that longer history of seizures and lower educational level would be associated with poorer performance on the neuropsychological test variables. Finally, it was expected that right temporal lobe volumes would predict verbal memory performance in women, but not men.

Method

Sample and Participant Selection

This study was a retrospective chart review of 163 consecutive adult outpatients with intractable epilepsy.[1] All patients underwent neuropsychological evaluation of their seizure disorder at Emory University's Center for Rehabilitation Medicine prior to January, 2006. Patients with a documented medical history of TBI, or with a mass lesion such as tumor, arteriovenous malformation, or heterotopia were excluded.

Demographic and clinical characteristics of the initial sample are presented in Table 1. The mean age was 35.9 (*SD* = 12.0, range 18 to 67). The sample was comprised of 89 females (55%) and 74 males (45%). Mean Full Scale IQ (assessed with either the Wechsler Adult Intelligence Scale – Third Edition [Wechsler, 1997] or the Wechsler Abbreviated Scale of Intelligence [Wechsler, 1999]) was 92.8 (*SD* = 17.4, range 52 – 134). Mean years of education was 13.4 (*SD* = 2.5, range 8 – 20 years). The racial composition of the sample was 79% Caucasian (*n* = 128), 18% African-American (*n* = 29), 1% Hispanic (*n* = 2), <1% Pacific Asian (*n* = 1), and 2% were classified as "other" (*n* = 3).

Table 1
Demographic and Clinical Characteristics of Participants *M* (*SD*)

	Initial sample (*N* = 163)	Final sample (*n* = 67)
Age	35.9 (12.0)	35.5 (11.7)
Sex (% male)	45	42
Years of Education	13.4 (2.5)	13.6 (2.3)
Full Scale IQ	92.8 (17.4)	93.9 (16.5)
Age at onset	18.2 (14.5)	16.3 (11.8)
Duration of epilepsy	17.5 (12.3)	18.8 (13.6)

[1] This study was reviewed and approved by both the Georgia State University Institutional Review Board and the Emory University Institutional Review Board.

With respect to seizure characteristics, the mean age of patients at the onset of their seizure disorder was 18.2 years (*SD* = 14.5, range 1-52 years). Duration of patients' seizure disorders ranged from 1 to 54 years (*M* = 17.5, *SD* = 12.3). Information on seizure frequency was not available. Patients were classified by epilepsy syndrome based on one or more of the following diagnostic techniques: inpatient EEG monitoring, MRI, PET, and intracarotid amobarbital procedure ("Wada test"). Based on these techniques, four epilepsy syndromes were identified in this sample: (a) 125 patients had a diagnosis of partial epilepsy with impairment of consciousness, (b) 6 patients had a diagnosis of partial epilepsy without impairment of consciousness, (c) 27 patients had a diagnosis of generalized convulsive epilepsy, and (d) 6 patients had a diagnosis of generalized nonconvulsive epilepsy.

Of these 163 patients, only those who had been administered all of the highest loading measures on an initial principal components analysis of the neuropsychological assessment battery were included in subsequent analyses. This resulted in a final sample of 67 patients. Demographic and clinical characteristics for these patients can be found above in table 1. The sample was comprised of 39 females (58%) and 28 males (42%) ranging in age from 18 to 66 (*M* = 35.5, *SD* = 11.7). Mean Full Scale IQ (assessed with either the Wechsler Adult Intelligence Scale – Third Edition or the Wechsler Abbreviated Scale of Intelligence) was 93.9 (*SD* = 16.5, range 57-130). The mean education level was 13.6 years (*SD* = 2.3, range 8-20). The racial composition of this sample was 81% Caucasian (*n* = 54), 18% African-American (*n* = 12), and 1% Pacific Asian (*n* = 1). Six patients were left-handed; the remaining 61 patients were

right-handed. Information was not available for most patients regarding their dominant hemisphere for language.

With respect to seizure characteristics for the final sample, the mean age of patients at the onset of their seizure disorder was 16.3 years (*SD* = 11.8, range 1-52 years). Duration of patients' seizure disorders ranged from 1 to 54 years (*M* = 18.8, *SD* = 13.6). All but 11 patients (84%) had an identified temporal lobe seizure focus or had been diagnosed with temporal lobe damage or dysfunction. With respect to epilepsy syndrome: (a) 55 patients were diagnosed with partial epilepsy with impairment of consciousness, (b) 3 patients were diagnosed with partial epilepsy without impairment of consciousness, and (c) 9 were diagnosed with generalized convulsive epilepsy (see Table 2). Information on areas of identified brain damage/dysfunction for the patients, based on EEG and/or neuroimaging, can be found in Table 2.

Fifty-nine patients (88%) were being treated with anti-seizure medications at the time of their neuropsychological evaluation. Information was not always available in the patient charts regarding the specific medications prescribed or whether patients were undergoing polytherapy versus monotherapy.

Table 2
Epilepsy Syndrome and Areas of Identified Brain Damage/Dysfunction for Final Sample

Area of damage/dysfunction	Epilepsy syndrome			
	Partial with IOC*	Partial without IOC*	Generalized convulsive	Total:
None	3	0	4	7
Right temporal	19	1	3	23
Left temporal	20	1	2	23
Bilateral temporal	10	0	0	10
Left frontal	1	0	0	1
Bifrontal	1	0	0	1
Right parietal	1	1	0	1
Total:	55	3	9	67

* IOC = impairment of consciousness

Neuropsychological Assessment and Measures

Participants were tested individually in a quiet room with as few distractions as possible. Tests were administered by a neuropsychology practicum student, intern, or fellow, or by a psychometrist trained in test administration. For the present study, measures were selected from an approximately 6-hour test battery that was typically administered during one testing session.

For the initial principal components analyses, test battery measures were chosen which were thought to represent the different domains of memory functioning in the theoretical model reviewed. These included measures of verbal episodic memory, figural memory, facial recognition memory, semantic memory, short-term memory, and spatial memory. The following tests were used: (a) the California Verbal Learning Test – Second Edition (CVLT-II; Delis, Kramer, Kaplan & Ober, 2000); (b) The Logical Memory, Verbal Paired Associates, Faces, Digit Span, and Spatial Span subtests from the Wechsler Memory Scale – Third Edition (WMS-III; Wechsler, 1997); (c) The Tombaugh administration of the Taylor Complex Figure (Tombaugh, Schmidt & Faulkner, 1992); (d) The Boston Naming Test (BNT; Goodglass & Kaplan, 1983); and (e) the Vocabulary subtest from either the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler, 1997) or the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). Published (normative sample referenced) *z*-score means and standard deviations for both the initial sample and the final sample on these variables can be found in Table 3. Mean test scores for the 96 patients who were excluded from the final sample did not differ significantly from the mean test scores for the 67 patients in the final sample. Detailed information about these measures follows.

Table 3
Sample Means and Standard Deviations on Principal Components Analysis Variables

Test	Initial sample (*N* = 163)		Final sample (*n* = 67)	
	M	*SD*	*M*	*SD*
WAIS-III Digit Span Forward	-0.76	1.02	-0.62	0.95
WAIS-III Digit Span Backward	-0.57	0.92	-0.47	0.96
WMS-III Spatial Span Forward	-1.06	0.78	-0.85	0.80
WMS-III Spatial Span Backward	-1.21	0.73	-1.24	0.80
WMS-III Faces Immediate Recognition	-0.42	1.12	-0.32	1.19
WMS-III Faces Delayed Recognition	-0.36	1.05	-0.29	1.08
WMS-III Logical Memory Immediate Recall	-0.31	1.07	-0.18	1.02
WMS-III Logical Memory Delayed Recall	-0.47	1.08	-0.34	1.04
WMS-III Verbal Paired Associates Imm. Recall	-0.67	1.12	-0.67	1.15
WMS-III Verbal Paired Associates Delayed Recall	-0.57	1.11	-0.55	1.02
Taylor Complex Figure 1st Recall	-1.06	1.19	-0.94	1.08
Taylor Complex Figure 2nd Recall	-1.74	1.76	-1.65	1.56
Taylor Complex Figure 3rd Recall	-2.58	2.80	-2.38	2.34
Taylor Complex Figure 4th Recall	-2.52	2.92	-2.14	2.38
Taylor Complex Figure Delayed Recall	-2.56	2.90	-2.22	2.59
CVLT Trial 1	-0.77	1.06	-0.69	0.95
CVLT Trial 2	-0.66	1.00	-0.54	0.94
CVLT Trial 3	-0.75	1.21	-0.63	1.21
CVLT Trial 4	-0.82	1.24	-0.60	1.28
CVLT Trial 5	-0.84	1.22	-0.69	1.24
CVLT Trials 1-5 Total Correct	-0.12	1.01	0.02	0.98
CVLT Short Delay Free Recall	-1.01	1.45	-0.81	1.37
CVLT Long Delay Free Recall	-1.10	1.44	-0.94	1.51
Boston Naming Test	-2.36	2.24	-2.15	2.22
WAIS-III or WASI Vocabulary	-0.53	2.05	-0.41	-2.11

Means and SDs are for published *z*-scores for all tests

California Verbal Learning Test – Second Edition (CVLT-II). The CVLT-II was included as a potential measure of verbal episodic memory. This test consists of five learning trials of a 16-word list followed by short and long delay recall trials. Eight variables from this measure were included in the principal components analysis: (a) number correct for each of five learning trials; (b) Total Correct for trials 1 through 5; (c) Short Delay Free Recall; and (d) Long Delay Free Recall. Because the CVLT-II manual does not provide norms for the total number correct for trials 1 through 5, *z*-scores for

that variable were calculated based on a subset of 115 participants from the normative sample that was used to assess the test-retest reliability of the CVLT-II (Woods, Delis, Cobb-Scott, Kramer, & Holdnack, 2006).

Split half reliability coefficients for this test (based on splitting immediate recall trials) ranged from .89 to .94 in a sample ranging in age from 16 to 89 (Delis et al., 2000). Test retest reliability for the five individual learning trials ranged from .57 to .82, and was .82 for total number correct in trials 1-5. For short and long delay free recalls, test-retest reliabilities were .81 and .88, respectively. The CVLT has been used successfully to discriminate between patients with right and left TLE (Loring et al., 2008). This test has also shown utility in both the measurement of memory decline after temporal lobectomy (Hermann et al., 1994) and in the prediction of memory decline based on presurgical performance (Davies, Bell, Bush, & Wyler, 1998).

Wechsler Memory Scale –Third Edition (WMS-III).

Logical Memory. Two additional potential measures of verbal episodic memory, the Logical Memory subtest and the Verbal Paired Associates subtest from the Wechsler Memory Scale –Third Edition (WMS-III), were included in this study. The Logical Memory subtest requires that patients learn two short stories that are presented orally. Two variables were selected for the principal components analysis, consisting of the Immediate Recall and Delayed Recall variables. In a sample of adults ages 18-69, split-half reliability coefficients (Spearman-Brown corrected) for the Logical Memory subtest were reported to range from .85 to .90 for the Immediate Recall variable, and from .73 to .84 for the Delayed Recall variable (Wechsler, 1997). Test-retest reliability

was reported to be .77 for both Immediate and Delayed Recall in a sample ranging in age from 16 to 54.

Verbal Paired Associates. The Verbal Paired Associates subtest requires that patients learn a list of word pairs that are presented orally. Two variables were selected for the principal components analysis, consisting of the Immediate Recall and Delayed Recall variables. Split-half reliability coefficients were reported to range from .91 to .95 for the Immediate Recall variable, and from .79 to .88 for the Delayed Recall variable (Wechsler, 1997). Test-retest reliability was .77 for the Immediate Recall variable and .73 for the Delayed Recall variable.

The Wechsler Memory Scales are said to be among the most reliable and best-validated measures of auditory-verbal memory (Wechsler, 1997). Scores on the Logical Memory subtest have been used successfully in previous research to discriminate patients with left TLE from patients with right TLE (Moore & Baker, 1996). In volumetric studies of patients with TLE, left hippocampal volume has been found to significantly correlate with performance on the Logical Memory Immediate and Delayed Recall variables (Reminger et al., 2004; Martin, et al., 1999); and left hippocampal volume minus left perirhinal volume has been found to predict scores on a Logical Memory immediate and delayed composite score (O'Brien et al., 2003). With respect to the Verbal Paired Associates subtest, left hippocampal volume has been found to predict significant variance in both Immediate and Delayed Recall scores in patients with TLE; and right hippocampal volume has been found to predict significant variance in the Delayed Recall score (Griffith et al., 2003).

Faces. Facial recognition memory was potentially assessed using the Faces subtest from the WMS-III. In this subtest, the patient is shown a series of photographs of unfamiliar faces and told to remember the faces. Immediate and Delayed Recognition is tested by showing patient another series of photographs consisting of novel and previously presented faces. The patient is asked to say “yes” if the photograph is of one of the faces (s)he was asked to remember earlier, or “no” if it is not. Both the Immediate and Delayed recognition scores were selected for the principal components analysis.

In a sample of adults ages 18-89, split-half reliability coefficients (Spearman-Brown corrected) were reported to range from .65 to .80 for the Immediate Recognition variable, and from .66 to .83 for the Delayed Recognition variable (Wechsler, 1997). Test-retest reliability was reported to be .64 for Immediate Recognition and .58 for Delayed Recognition in a sample ranging in age from 16 to 54. In a sample of epilepsy patients, Delayed Recognition has been found to correlate significantly with right hippocampal volume (Bell, 2004).

Spatial Span. Spatial memory was potentially assessed using the Spatial Span task from the WMS-III. This subtest consists of two tasks, Spatial Span Forward and Spatial Span Backward. During the Spatial Span Forward task, an array of identical blocks is placed between the examiner and the patient. The examiner points to a sequence of blocks and then the patient is asked to point to the blocks in the same order. The Spatial Span Backward task is identical to Spatial Span Forward except the participant is asked to point to the blocks in the reverse order from the original presentation. The sequences are presented in pairs and range in length from 2 to 8

blocks. Maximum span forward and maximum span backward were used for the principal components analysis. Test-retest reliability was .60 for the forward span total score, and .59 for the backward span total score in a sample ranging in age from 16 to 54 (Wechsler 1997).

Two studies were found which examined the performance of TLE patients on this subtest. In the most recent study, Wilde et al. (2001) found no significant differences between right and left TLE patients on this task. In the earlier study, Rausch and Ary (1990) found that patients who had undergone temporal lobectomy did not show impairment on this task. Thus, they concluded that mesial temporal lobe structures are not critical for this task. This is consistent with the classification of this task as a test of short-term memory and/or attention. However, for lack of a better measure, it is hypothesized that this test might also tap spatial episodic memory for the purposes of the present study.

Taylor Complex Figure. The Tombaugh administration of the Taylor Complex Figure was selected as a potential measure of figural episodic memory (Tombaugh et al., 1992). This test requires the patient to draw a complex design from memory, with the expectation that (s)he will recall an increasing number of details with each timed exposure to the figure over four learning trials. Five variables were selected for the factor analysis: trials 1 – 4 recall scores, and delayed recall. In a sample of 407 adults ranging in age from 20 to79, internal consistencies (Chronbach alphas) for the first learning trial, the last learning trial, and the delay trial were .92, .94, and .94 (Tombaugh, et al., 1992).

Although no studies were found that examine the performance of TLE patients on this task, some studies have found that a similar visuospatial memory task, the Rey-Osterrieth Complex Figure, distinguishes between patients with right and left TLE (Frank & Landeira-Fernandez, 2008; Breier, et al., 1996; Loring, Lee, & Meador, 1988). Despite the lack of research on the use of this measure with TLE patients, the Tombaugh administration of the Taylor Complex Figure is believed to be more comparable than the Rey-Osterrieth figure to the verbal episodic memory tasks administered in this study. Specifically, as with the verbal episodic memory tasks included in this study, the Taylor Complex Figure: (a) consists of several learning trials, (b) exposure to the material is time-limited, and (c) patients are told in advance that they will be asked to recall the material again later. In contrast, during administration of the Rey-Osterrieth figure: (a) test-takers are not warned they will have to recall the figure, (b) the figure is only presented once prior to the recall trials, and (c) exposure to the figure varies depending upon the time it takes for test-takers to copy it.

Boston Naming Test. The Boston Naming Test (BNT; Goodglass & Kaplan, 1983) was included in this study as a potential measure of verbal semantic memory. The BNT is a confrontation naming task in which the patient is presented with a series of line drawings ranging from simple, high-frequency vocabulary (e.g., “chair”) to low-frequency words (e.g., “calipers”). The patient is given credit for items that are correctly names within 20 seconds. Test-retest reliability after 8 months was reported to be .94 in a sample of 51 adult epileptics (Sawrie, Chelune, Naugle, & Lüders, 1996). Scores on this measure have been used successfully in previous research to discriminate patients with left TLE from patients with right TLE (Busch, Frazier, Lampietro, Chapin, & Kubu,

2009; Loring et al., 2008; Oyegbile, et al., 2004; Raspall et al., 2005; Schefft, Testa, Dulay, & Yeh, 2003). It has also been found that epilepsy patients with hippocampal atrophy have significantly lower scores on this test than patients without hippocampal atrophy (Alessio et al., 2004).

Wechsler Intelligence Scales.

Vocabulary. The Vocabulary subtest from the Wechsler Abbreviated Scale of Intelligence (WASI) or the Wechsler Scale of Adult Intelligence – Third Edition (WAIS-III) was included as another potential measure of semantic memory. This subtest assesses the patient's ability to define words. Test-retest reliability for this subtest ranged from .90 to .98 in a sample ranging in age from 17 to 89. The split-half reliability coefficient for this subtest was found to be .83. in a sample of 27 individuals with temporal lobe epilepsy (Zhu, Tulsky, Price & Chen, 2001). An earlier version of this subtest (from the WAIS-R) has been shown to statistically discriminate between patients with left and right TLE (Hermann et al., 1995).

Digit Span. Short-term verbal memory was potentially assessed using the Digit Span subtest. This task consists of two portions: Digit Span Forward and Digit Span Backward. In the Digit Span Forward task, the examiner verbally presents a series of random digits to the patient, who is then asked to repeat the digits in order. The Digit Span Backward task is identical to the forward span task except the patient is required to produce the digits in the reverse order to that presented. Items are presented in pairs and range from 2 to 9 digits in the Digit Span Forward task and from 2 to 8 digits items in the Digit Span Backward task. Longest span forward and longest span backward

were used for the principal components analysis. Test retest stability coefficients for this test were in the .80s in a sample ranging in age from 16 to 89 (Wechsler, 1997).

No published studies were found which examined WAIS-III Digit Span performance in patients with TLE. Two studies were found which examine TLE patients' performance on the Digit Span subtest of the original WAIS. In the most recent study, no significant differences were reported between right and left TLE patients (Schneider, Nowack, Fitzgerald, Janati & Souheaver, 1993). In the earlier study, Kupke and Lewis (1986) reported that the WAIS Digit Span subtest statistically discriminated between control subjects and "moderately impaired" but not "mildly impaired" patients with epilepsy. However, 80% of these "moderately impaired" patients had a history of distinct neuropathology such as head trauma, brain tumor, neurodegenerative disease, or history of lobectomy. In addition, a third of the "moderately impaired" patients had signs of anticonvulsant toxicity. Thus, it is unclear whether the observed differences were related to the patients' temporal lobe epilepsy, or to medical factors separate from the patients' seizure disorders.

Brain Volume Assessment (for Validation of Clusters)

For a subset of patients, MRI scans had been acquired in the course of their routine clinical care. Often, but not always, these scans were obtained as part of an evaluation for temporal lobectomy. When MRI scans were available, brain volumes of selected temporal lobe structures (left and right hippocampi, left and right perirhinal cortices, and left and right anterior temporal lobes) were calculated for each patient using MRI volumetry. MRI volumetry is an index of neuronal volume, and has been shown to be a more accurate measure of brain disease than qualitative MRI readings

made by trained neurologists (Cendes et al., 1993). Inclusion criteria for MRI scans included: 1) digitally recorded, high-resolution, T1-weighted, 3-D gradient echo scans in a coronal plane orientation (512 x 512 image size); 2) slice thicknesses less than or equal to 2 mm; and 3) scans taken within 18 months of the neuropsychological assessment. Twenty-six scans met the above inclusion criteria. All scans were obtained using a Phillips Gyroscan Intera 1.5 –Tesla scanner (Philips International, Eindhoven, Holland), and were acquired within 17 months of the neuropsychological assessment (*M* = 4.6, *SD* = 4.5, range 0 – 17 months). The sample ranged in slice thickness from 1.0 mm to 2.0 mm.

In volumetric studies, it is common to restrict the range of MRI slice thicknesses in one sample to 0.5 mm. This is because a large disparity in slice thicknesses makes direct comparison of MRI scans problematic. For example, 1.0 mm scans produce twice as many samples as 2.0 mm scans which effectively doubles obtained brain volumes. To address this issue, all obtained brain volumes were multiplied by MRI slice thickness (as per Watson et al., 1992). This method was chosen to help compensate for the small available sample of MRIs in the present study. Because this method involves some estimation of brain volume, particularly with thicker MRI slices, it introduces some error into the analyses. However, because the estimation is based on samples taken at regular intervals throughout the brain structures of interest, it is likely to be reasonably accurate.

For comparison purposes, MRI scans were also divided into two groups for volumetric analysis. The first group consisted of: 1) scans with 1.0 mm slice thicknesses in which every other slice was measured, and 2) scans with 2.0 mm slice

thicknesses (“slicegroup 1;” *n* = 15). The second group consisted of scans with slice thicknesses between 1.25 mm and 1.5 mm (“slicegroup 2;” *n* = 11). The results of these analyses were not significantly different from the analyses of all the MRI scans combined into one group and multiplied by slice thickness. Therefore, for the sake of brevity, these results are contained in Appendix A.

To control for individual differences in total brain volume, all MRI volumes were divided by the patient’s coronal intracranial volume (ICA) at the level of the anterior commissure. This method has been shown to be effective at reducing the variability in medial temporal lobe volume measurements (Gold & Squire, 2005).

The number of slices available for analysis varied, depending upon the structure and slice thickness; however, a minimum of 10 slices were analyzed per structure. In previous research, it has been found that a sampling frequency of 6 to 10 slices is needed to achieve 95% accuracy in volume measures, depending upon whether the structure is “regular” or “irregular” (O’Brien et al., 2003). Thus, sufficient slices were obtained in this study to achieve a high degree of accuracy.

Six primary regions of interest were analyzed: 1) bilateral hippocampi, 2) bilateral perirhinal cortices, and 3) bilateral anterior temporal lobes. In addition, the following combinations of primary regions of interest were analyzed: 1) right plus left hippocampus, 2) right minus left hippocampus, 3) right plus left perirhinal cortex, 4) right minus left perirhinal cortex, 5) right plus left anterior temporal lobe, 6) right minus left anterior temporal lobe, 7) left hippocampus plus left perirhinal cortex, 8) right hippocampus plus right perirhinal cortex, 9) the sum of right hippocampus and right perirhinal cortex minus the sum of left hippocampus and perirhinal cortex, 10) the sum

of bilateral hippocampi and perirhinal cortices, 11) the sum of right hippocampus, perirhinal cortex, and anterior temporal lobe, 12) the sum of left hippocampus, perirhinal cortex, and anterior temporal lobe, 13) the sum of right hippocampus, perirhinal cortex, and anterior temporal lobe minus the sum of left hippocampus, perirhinal cortex, and anterior temporal lobe, 14) the bilateral sum of hippocampi, perirhinal cortices, and anterior temporal lobes. Images were analyzed using MRIcro software version 1.40 (copyright Chris Rorden 1999-2005). This program allows for manual tracing of the brain regions of interest (ROIs).

Volumetric analyses of the regions of interest were performed by the author, who was blind to epilepsy diagnosis. To establish intra-rater reliability, the author retraced the ROI volumes of 5 scans (19% of the sample) on separate occasions. Based on these multiple tracings, intra-rater reliabilities (both intraclass correlations and Pearson-product-moment correlations) ranged from 0.96 to 1.00 (see Table 4).

Table 4
Intra-Rater Reliabilities for the Six Regions of Interest (ROIs)

ROI	Pearson product-moment correlation	Intraclass correlation
left hippocampus	0.99	0.99
right hippocampus	0.99	0.99
left perirhinal cortex	1.00	0.99
right perirhinal cortex	0.97	0.97
left anterior temporal lobe	0.98	0.97
right anterior temporal lobe	0.96	0.96

Because a second rater trained in volumetric analysis was not available, interrater reliabilities could not be established. However, in previous research it has been found that intraobserver and interobserver variability were of “minor importance” in volumetric analysis (Insausti et al., 1998). Instead, biological variations accounted for most of the variability in brain volume.

Definition of hippocampal boundaries. The hippocampal region of interest included the entire hippocampal formation (including the subiculum, the dentate gyrus, and the hippocampus proper) as these structures are nearly indistinguishable on MR images. Boundaries for this structure were based on those provided in a 2001 Power Point presentation by Samantha L. Free (National Society for Epilepsy MRI unit, Epilepsy Research Group, Institute of Neurology, University College, London). In addition, feedback on tracing accuracy on a sample of scans was provided by a researcher experienced in volumetric analysis on a sample of scans (Leonardo Bonilha, M.D., Ph.D., of the Medical University of South Carolina).

Tracing began rostrally where the hippocampus first appeared below the amygdala. In the most anterior slices, the CSF in the temporal horn was used to mark the lateral and superior boundaries (between hippocampus and amygdala). The medial and inferior boundaries consisted of the curve of white matter underlying the hippocampus and extending over to the CSF of the ambient cistern. As the uncus began to disappear, the medial boundary became the CSF. Moving posteriorly, the white matter of the alveus was included in the superior ROI if it appeared integral to the hippocampus. If the alveus was difficult to separate from the overlying white matter, it was excluded from the ROI. In the most posterior slices, the white matter of the parahippocampal gyrus was used as the inferior boundary of the hippocampal ROI. The white matter of the temporal stem and/or the CSF in the temporal horn was used as the lateral boundary of the ROI. The CSF of the ambient cistern continued to serve as the medial boundary. In the most posterior slices, the fornices provided the superior limit

of the ROI. Tracing ended posteriorly on each side with the slice in which the ipsilateral fornix was longest.

Definition of perirhinal cortex boundaries. A detailed description of the measurement protocol used in tracing the perirhinal cortex can be found in Insausti et al. (1998). Briefly, tracing began in the slice closest to 2 mm anterior to the limen insulae. The ventrolateral border, prior to the appearance of the limen insulae, was the lateral edge of the collateral sulcus. At the level of the limen insulae, the most medial point of the parahippocampal gyrus was used as the dorsomedial border. The lateral border, in most cases, was at the lateral edge of the collateral sulcus (see Insausti et al., 1998, for variations based on anatomical differences). Tracing ended 4 mm posterior to the posterior limit of the gyrus intralimbicus. Here the medial border was drawn where an imaginary line from the white matter underlying the presubiculum and parasubiculum would extend medially to touch the pial surface. The lateral boundary was the same as that used in more rostral slices.

Definition of anterior temporal lobe boundaries. Tracing began caudally at the first slice anterior to the perirhinal cortex ROI to prevent overlap in ROIs. Tracing ended rostrally at the most anterior slice in which the boundaries of the temporal lobe could be clearly visualized.

Statistical Analyses

Principal components analysis. To evaluate the underlying measurement model for this study, neuropsychological test scores were analyzed via a principal

components analysis with varimax rotation. This analysis was conducted using the SPSS 15.0 for Windows software package (copyright SPSS, Inc., Chicago, IL 1989-2006).

Sample-referenced *z*-scores were chosen over raw scores for this analysis because their common metric facilitated comparison of performance across the various cognitive domains. These scores were found to have reasonably normal distributions, and were free from outliers (i.e., the *z*-scores ranged from -3.03 to 3.09).

It was expected that 6 components would emerge representing: short-term memory, verbal episodic memory, verbal semantic memory, figural episodic memory, facial recognition memory, and spatial memory. However, the analysis resulted in only five components with eigenvalues greater than 1. These five components appeared to correspond to the domains of memory listed above with the exception of a spatial memory component. Indicators of factorability, including Bartlett's Test of Sphericity and negative partial correlations, were good. Furthermore, inspection of the residuals suggested that the obtained solution was good.

The two highest loading variables on each of the five components (in order of variance accounted for) were: (a) CVLT Trials 1-5 total and CVLT Long Delay Free Recall; (b) Taylor Complex Figure 3rd recall and Taylor Complex Figure 4th recall; (c) Digit Span Forward and Digit Span Backward; (d) WMS-III Faces Delayed Recognition and WMS-III Faces Immediate Recognition; (e) WMS-III Logical Memory Immediate Recall and Boston Naming Test. The loadings of these variables obtained from the rotated component matrix are shown below in Table 5. The highest loading measure

from each component was used as classification attributes for subsequent cluster analyses; and the second highest loading measure was used for cross-validation studies.

Table 5
Highest Loading Measures on the Five PCA Components

Test	Component				
	1	2	3	4	5
CVLT Trials 1-5 Total Correct	**0.920**	0.174	0.172	0.237	0.075
CVLT Long Delay Free Recall	**0.848**	0.148	0.158	0.194	0.242
Taylor Trial 3	0.154	**0.934**	0.152	0.130	0.045
Taylor Trial 4	0.134	**0.930**	0.103	0.114	0.046
Digit Span Forward	0.131	-0.005	**0.816**	0.154	0.036
Digit Span Backward	0.233	0.144	**0.765**	0.100	0.177
Logical Memory Immed. Recall	0.498	0.246	0.101	**0.737**	0.071
Boston Naming Test	0.240	0.210	0.254	**0.688**	0.261
Faces Delayed Recog.	0.158	0.117	0.180	0.246	**0.758**
Faces Immediate Recog.	0.045	0.132	0.128	0.297	**0.752**

Cluster analysis. Cluster analyses were conducted using the Clustan Graphics 8.02 software package (copyright 2005 by Clustan Ltd., Edinburgh, Scotland). Two hierarchical agglomerative algorithms were used (Ward's method and average linkage) to ensure that classification of subjects was internally consistent and reliable (Morris et al., 1998). Squared Euclidean distance was selected as the index of pairwise similarity-dissimilarity between subject profiles. Euclidean distance or squared Euclidean distance is used predominantly in published health psychology research (Clathworthy, Buick, Hankins, Weinman, and Horne, 2005). This method was chosen over Pearson's correlation, the other similarity measure commonly used in research, because it takes into account elevation of scores rather than just the profile of scores when grouping subjects.

There is no well-validated or standard approach to determining the optimal number of clusters in a cluster-analytic solution. Therefore, several approaches were

used to decide on the optimal number of clusters. Initially, a range of optimal clusters was identified by examining the agglomeration schedule for both clustering methods. Only late stages in the hierarchies were examined for two reasons: 1) to keep the number of clusters reasonably small, and 2) to maintain reasonable sample sizes within each cluster. The hierarchies were examined for relatively large increases in the sum of squares coefficients after relatively small increases at previous stages. A sudden jump in the sum of squares coefficient is a sign that combination of the two previous clusters created a heterogeneous cluster that contains extensive variance (Morris, Blashfield & Satz, 1981). The clusters preceding these jumps were then selected for further analysis.

After a range of optimal clusters was identified for each clustering method, the k-means iterative partitioning method was used to optimize the results (as per Milligan, 1980). Iterative partitioning methods start with the multiple initial solutions and reevaluate each individual within each cluster to determine whether that individual best fits into the original cluster or another cluster. Relocation through iterative partitioning is desirable when using hierarchical agglomerative methods because hierarchical agglomerative methods do not correct errors in the placement of an individual within an early forming cluster, even though the patient may fit a later forming cluster much better (Morris et al., 1998). Once these relocation evaluations were completed, chi square analyses were used to compare the results from the two clustering methods (Morris et al., 1998).

Concordance between the two clustering methods was then calculated by tallying the number of patients assigned to the same cluster for each method. Good

concordance was defined as 80% or greater agreement between the two clustering methods. Clusters having good concordance were selected for further analyses. Because optimal cluster sizes were the same for both Ward's method and the average linkage method, and because both methods were found to have good overall concordance, clusters obtained using Ward's method with k-means iterative partitioning were selected for the remaining analyses.

After optimal cluster sizes had been identified, patient profiles within and across clusters were visually inspected and characterized in terms of their neuropsychological deficits. Mild impairment was defined as a published (normative-sample-referenced) *z*-score between -1.0 and -1.99. Moderate impairment was defined as a *z*-score between -2.0 and -2.99. Severe impairment was defined at a *z*-score below or equal to -3.0. For each patient, the number of impaired scores (a *z*-score of -1.0 or less) on the five neuropsychological classification variables was tallied. Patients were coded as having: a) no deficits, b) mild to moderate deficits (impairment on 1 or 2 tests), or c) moderate to severe deficits (impairment on 3 to 5 tests. Pearson chi-square analyses were then used to determine whether the clusters differed in terms of number of deficits.

A series of multivariate analyses of variance (MANOVAs) was used to determine whether clusters significantly differed on the five classification variables. For these profile comparisons, *z*-scores based on each test's normative sample were used rather than *z*-scores based on the original epilepsy sample. This is because *z*-scores based on the epilepsy sample would have masked or minimized the presence of deficits relative to a normal population.

Assessment of internal and external validity of clusters. One-way analyses of variance with Bonferroni post-hoc pairwise comparisons were used to compare clusters on demographic composition (age, and education level) and on clinical seizure features (age at onset and duration of epilepsy). Pearson chi-square analyses were used to determine whether clusters differed significantly in terms of sex. It should be noted that, due to the small size of this sample, some of these analyses resulted in a violation of chi-square rules (e.g., in some cases >20% of cells had and expected value of less than 5 and/or the minimum expected count was less than 1).

Additionally, MRI volumetric data were analyzed for cluster members when available. It was hypothesized that cluster differences in seizure foci would result in significant differences in ROI brain volumes. Thus, patient clusters were subjected to a series of ANOVA's with Bonferroni post-hoc tests to determine whether the groups significantly differed on the MRI volumetric measures as predicted.

Cluster analysis of alternative classification variables. The cluster analyses described above were repeated using the second-highest loading neuropsychological test scores from the initial principal components analysis. Cluster assignment on these alternative classification variables was then compared to cluster assignment on the original classification variables. As the original and the alternative classification variables were highly correlated, this was not a strong test of internal validity. Nevertheless, this approach was superior to an evaluation based solely on the original classification variables.

Comparison of cluster analysis and neuropsychological classification of patients. Based on patients' patterns of performance on the 25 neuropsychological test variables used in the initial principal components analysis, the author independently sorted patients into four groups: 1) verbal memory deficits only, 2) visuospatial memory deficits only, 3) both verbal and visuospatial memory deficits, and 4) neither verbal nor visuospatial memory deficits. Pearson's chi-square was used to assess whether the neuropsychological classification of patients was related to how patients were clustered using Ward's method (k-means refined). In addition, MANOVA was used to determine whether the groups obtained by neuropsychological classification differed significantly on the five classification variables used for the initial cluster analysis.

Comparison of cluster analysis and neuroradiological classification of patients. Patients were sorted into 4 groups based on neurologists' and/or radiologists' localization interpretations of EEG and/or neuroimaging results. These groups were: 1) left temporal lobe damage/dysfunction, 2) right temporal lobe damage/dysfunction, 3) bilateral temporal lobe damage/dysfunction, and 4) no temporal lobe damage/dysfunction. Pearson's chi-square was used to assess whether neuroradiological classification of patients was related to how patients were clustered using Ward's method (k-means refined). In addition, MANOVA was used to determine whether the groups obtained by neuroradiological classification differed significantly on the five classification variables used for the initial cluster analysis.

To assess the validity of the neuropsychological and neuroradiological classifications of patients, brain volumes for these groups were also analyzed using one-way analysis of variance with Bonferroni post-hoc pairwise comparisons.

Results

Cluster Analysis

Selection of optimal cluster size. The highest loading test variables from each of the five components obtained from an initial principal components analysis were used for cluster analyses. These variables were: (a) CVLT Trials 1-5 total; (b) Taylor Complex Figure 3rd recall; (c) Digit Span Forward; (d) WMS-III Faces Delayed Recognition; (e) WMS-III Logical Memory Immediate Recall. Inspection of the agglomeration schedules for the two methods resulted in the same three potential solutions for each method (cluster sizes 2, 3, and 6). After k-means iterative partitioning, concordance in classification of patients was assessed for the two methods. Concordance was found to be 100% for both the 2 and 3 cluster solutions. For the 6-cluster solutions, 84% (n = 56) of patients were assigned to the same cluster using both Ward's method (k-means refined) and Average Linkage method (k-means refined). Thus, the two methods had good concordance at the cluster sizes.

Due to the high concordance between Ward's method and the Average Linkage method after k-means iterative partitioning, and for simplification in presenting results, the remaining analyses are presented only for the clusters obtained using Ward's method.

Cluster performance on classification and demographic variables.

Two-cluster solution. In the 2-cluster solution, cluster 1 exhibited mild impairment on the Taylor Complex Figure 3rd recall variable, whereas cluster 2 exhibited severe impairment on that variable. Though the two clusters performed within normal limits on the other four neuropsychological variables, cluster 2 consistently performed

one or more standard deviations below cluster 1. Cluster means and standard deviations on the classification variables are presented in Table 6. In addition, profiles for the two clusters can be found in Figure 1.

Pearson chi-square analysis indicated that patients in cluster 1 had fewer test scores in the impaired range ($z \leq -1.00$) than patients in cluster 2 ($\chi^2 = 36.3$, $df = 2$, $p < .001$). Specifically, inspection of the contingency table revealed that all fifteen patients who were classified as having no deficits were placed in cluster 1, whereas 24 out of 25 patients classified as having moderate to severe deficits (i.e., impairment on 3 to 5 tests) were placed in cluster 2. The 27 patients classified as having mild to moderate deficits (i.e., impairment on 1 or 2 tests) were more evenly distributed between cluster 1 ($n = 15$) and cluster 2 ($n = 12$).

Table 6
Means of Two Clusters on Neuropsychological Tests *M* (*SD*)

Test variable	Cluster 1 ($n = 31$)	Cluster 2 ($n = 36$)
CVLT Trials 1-5 Total Correct*	0.84 (0.44)	-0.70 (0.71)
Taylor Complex Figure, Trial 3*	-1.02 (1.47)	-3.54 (2.33)
WMS-III Digit Span Forward*	-0.19 (0.80)	-0.98 (0.93)
WMS-III Logical Memory Immediate recall*	0.46 (0.72)	-0.74 (0.92)
WMS-III Faces Delayed recognition*	0.31 (1.08)	-0.82 (0.78)

*Differences were significant between clusters, $p < .001$

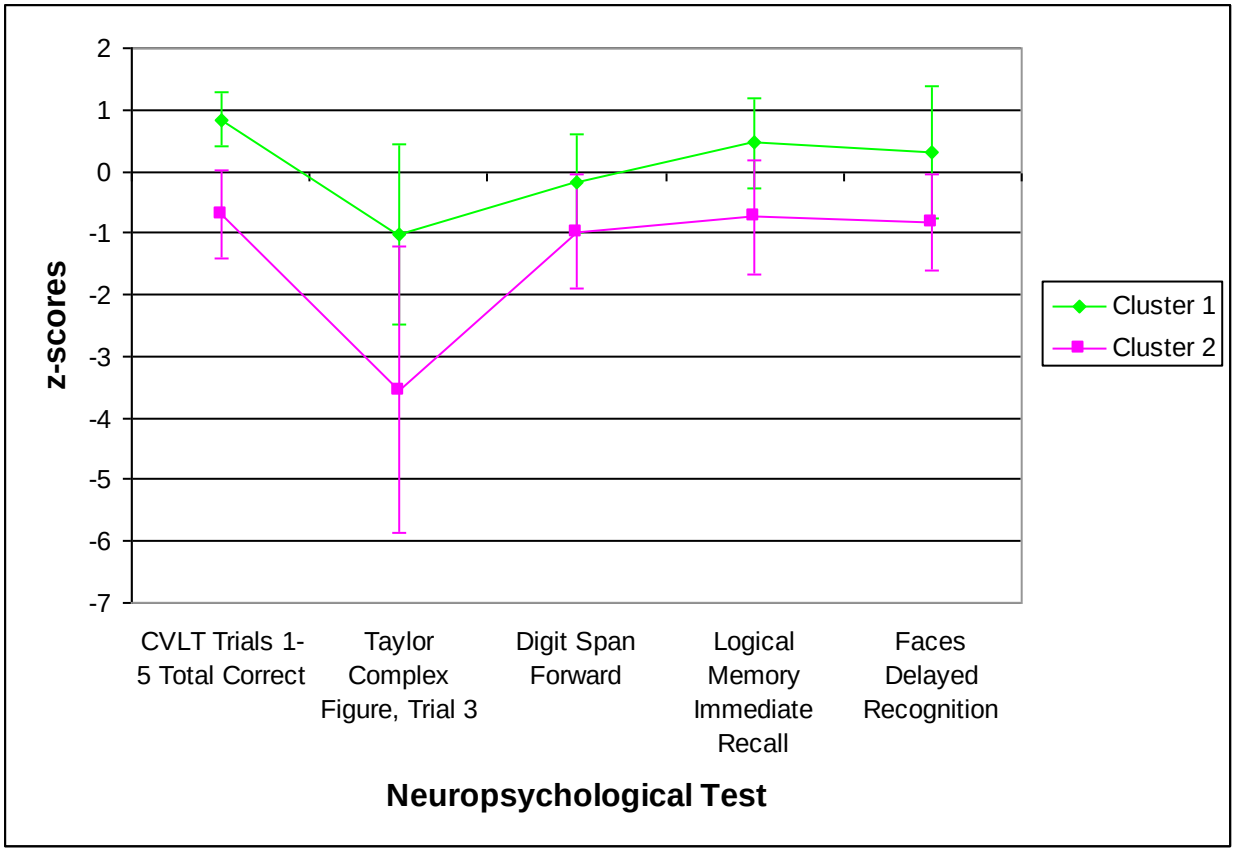

Figure 1. Performance of two clusters on classification variables.

A one-way MANOVA was used to compare the two cluster groups on the five classification variables. A significant effect of group was obtained, $F(5, 61) = 39.99$, $p < .001$; Pillai's Trace = .77; partial eta squared = .77. Using a Bonferroni adjusted alpha level of 0.01, univariate effects were significant for all five classification variables. Specifically, cluster 1 scored significantly higher on all five neuropsychological variables than cluster 2 ($p < 0.001$).

With respect to demographic and seizure variables, patients in cluster 1 (the "higher functioning" cluster) had significantly more years of education, $F(1, 65) = 5.52$, $p = .02$, and significantly higher IQ scores, $F(1, 65) = 19.69$, $p <.001$, than patients in cluster 2. Means and standard deviations are presented in Table 7. There was also a trend toward patients in cluster 2 (the "lower functioning" cluster) having a longer

duration of illness than patients in cluster 1, $F(1, 64) = 3.30$, $p = .07$. The two clusters did not differ with respect to current age or age at onset of their seizure disorder. Pearson's chi-square analysis indicated that there was a significant relationship between cluster assignment and sex ($\chi^2 = 3.86$, $df = 1$, $p = .05$). Specifically, inspection of the contingency table revealed that 19 of the 28 (68%) males were assigned to cluster 2. Females were more evenly distributed between cluster 1 and cluster 2 (56% and 44%, respectively).

Table 7
Two Cluster Demographic and Seizure Characteristics *M* (*SD*)

	Cluster 1 (*n* = 31)	Cluster 2 (*n* = 36)
Age	33.35 (11.21)	37.25 (11.98)
Sex (% male)*	29	53
Years of Education*	14.29 (2.13)	13.00 (2.33)
IQ*	102.5 (12.05)	86.61 (16.43)
Age at onset	17.10 (11.25)	15.71 (12.44)
Duration of epilepsy (yrs)	15.53 (13.26)	21.54 (13.51)

* Differences were significant between clusters, $p \leq .05$

Three-cluster solution. In the 3-cluster solution, cluster 1 exhibited mild impairment on the Taylor Complex Figure 3rd Recall variable, and average performance on the other four neuropsychological variables. Cluster 2 demonstrated moderate impairment on the Taylor Complex Figure 3rd Recall variable and mild impairment on both Delayed Facial Recognition and Digit Span Forward. Cluster 3 demonstrated severe impairment on the Taylor Complex Figure 3rd Recall variable and mild impairments on the Logical Memory Immediate Recall and the CVLT Trials 1-5 Total Correct variables. (see Table 8). Profiles for the three clusters can be found in Figure 2.

Pearson chi-square analysis indicated that patients in cluster 1 had fewer test scores in the impaired range ($z \leq -1.00$) than patients in clusters 2 and 3 ($\chi^2 = 41.23$, $df = 4$, $p < .001$). Specifically, inspection of the contingency table revealed that all fifteen

patients who were classified as having no deficits were placed in cluster 1, whereas 16 out of 25 (72.7%) patients classified as having moderate to severe deficits (i.e., impairment on 3 to 5 tests) were placed in cluster 3. The remaining 9 patients with moderate to severe deficits were placed in cluster 2. The 27 patients classified as having mild to moderate deficits (i.e., impairment on 1 or 2 tests) were more evenly distributed between the three clusters (*n* = 13, 8, and 6, respectively).

Table 8
Means of Three Clusters on Neuropsychological Tests *M* (*SD*)

Test variable	Cluster 1 (*n* = 28)	Cluster 2 (*n* = 17)	Cluster 3 (*n* = 22)
CVLT Trials 1-5 Total Correct*	0.82 (0.43)	0.02 (0.74)	-1.00 (0.61)
Taylor Complex Figure, Trial 3*	-1.07 (1.52)	-2.29 (2.20)	-4.10 (2.27)
WMS-III Digit Span Forward*	-0.11 (0.79)	-1.47 (0.56)	-0.60 (0.94)
WMS-III Logical Memory Imm. Recall*	0.49 (0.75)	0.04 (0.33)	-1.21 (0.86)
WMS-III Faces Delayed Recognition*	0.45 (1.00)	-1.06 (0.59)	-0.65 (0.88)

*Differences were significant between clusters, *p* <.001

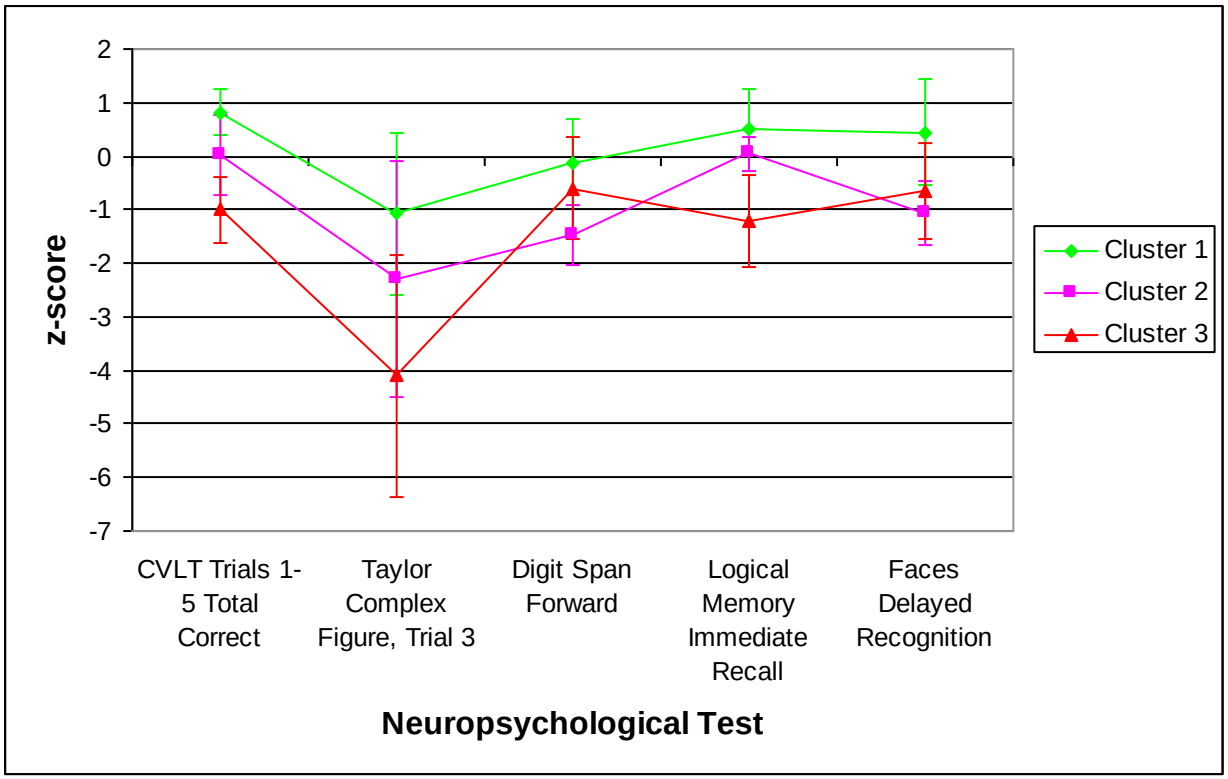

Figure 2. Performance of three clusters on classification variables.

A one-way MANOVA was used to compare the three cluster groups on the five classification variables (see Table 9). A significant effect of group was obtained, $F(10, 122) = 19.58$, $p < 0.001$, Pillai's Trace = 1.23, partial eta squared = .62. Using a Bonferroni adjusted alpha level of 0.01, univariate effects were significant for all five classification variables ($p < 0.001$; Bonferroni post-hoc comparisons can be found in Appendix B).

Table 9
Significant Differences on Classification Variables for 3-Cluster Solution

Test variable	*df*	*F*	Significance
CVLT Trials 1-5 Total Correct	2,64	61.13	0.001
Taylor Complex Figure, Trial 3	2,64	14.54	0.001
WMS-III Digit Span Forward	2,64	15.43	0.001
WMS-III Logical Memory Immediate recall	2,64	36.2	0.001
WMS-III Faces Delayed recognition	2,64	18.51	0.001

Specifically, patients in cluster 1 scored significantly higher than patients in clusters 2 and 3 on the CVLT Trials 1-5 Total variable. Patients in cluster 1 also scored higher than patients in cluster 2 on the Digit Span Forward and the Faces Delayed Recognition variables, and they scored higher than patients in cluster 3 on the Taylor Figure 3rd Recall variable and the Logical Memory Immediate Recall variable. Patients in cluster 2 scored higher than patients in cluster 3 on four of the five classification variables (CVLT Trials 1-5 Total, Digit Span Forward, Taylor Figure 3rd Recall, and Logical Memory Immediate Recall).

With respect to demographic and seizure variables, patients in cluster 1 had significantly more years of education than patients in cluster 3, $F(2, 64) = 3.50$, $p = .04$. Means and standard deviations are presented in Table 10. Patients in cluster 1 also had significantly higher IQ scores than patients in cluster 2 and cluster 3, $F(2, 64) = 10.12$, $p < .001$. Chi square analysis of the three clusters showed that there was a

significant relationship between cluster assignment and sex (χ^2 = 9.70, *df* = 2, *p* = .01). Inspection of the contingency table showed that 15 of 28 males (54%) were assigned to cluster 3, whereas only 7 out of 39 females (18%) were assigned to that cluster. The three groups did not significantly differ in terms of age, age at onset of epilepsy, or duration of epilepsy.

Table 10
Three Cluster Demographic and Seizure Characteristics *M* (*SD*)

	Cluster 1 (*n* = 28)	Cluster 2 (*n* = 17)	Cluster 3 (*n* = 22)
Age	33.89 (11.47)	36.59 (11.50)	36.55 (12.46)
Sex (% male)*	32	24	68
Years of Education*	14.43 (2.15)	13.24 (1.68)	12.82 (2.67)
IQ*	103.04 (12.12)	90.76 (14.45)	84.82 (17.40)
Age at onset	17.84 (11.02)	14.00 (13.00)	16.32 (12.16)
Duration (years)	15.27 (13.62)	22.59 (13.86)	20.22 (13.03)

* Differences were significant between clusters, *p* < .05

Six-cluster solution. In the 6-cluster solution, only patients in cluster 3 scored within normal limits on all five neuropsychological variables (see Table 11). Patients in clusters 1 and 2 demonstrated isolated moderate or mild deficits on the Taylor Complex Figure 3rd Recall variable, respectively. Cluster 4 demonstrated severe deficits on the Taylor Complex Figure 3rd Recall variable and mild deficits in both Delayed Facial Recognition and Digit Span Forward. Cluster 6 demonstrated severe deficits on the Taylor Complex Figure 3rd Recall variable and mild deficits on both the CVLT Trials 1-5 variable and the Logical Memory Immediate Recall variable. Finally, patients in cluster 5 demonstrated isolated mild deficits on Digit Span Forward. Profiles for the 6 clusters can be found in Figure 3.

Table 11
Comparison of six clusters performance on neuropsychological tests *M* (*SD*)

Test variable	Cluster 1 (*n* = 10)	Cluster 2 (*n* = 14)	Cluster 3 (*n* = 8)	Cluster 4 (*n* = 10)	Cluster 5 (*n* = 11)	Cluster 6 (*n* = 14)
CVLT Trials 1-5 Total Correct*	0.02 (0.58)	0.71 (0.38)	1.12 (0.30)	0.48 (0.73)	-0.53 (0.76)	-1.21 (0.53)
Taylor Complex Figure Trial 3*	-2.46 (1.82)	-1.39 (1.27)	-0.40 (1.05)	-3.24 (2.30)	-0.98 (1.58)	-4.91 (2.25)
Digit Span Forward*	0.54 (0.38)	-0.80 (0.48)	0.56 (0.39)	-1.22 (0.63)	-1.32 -0.69	-0.94 (0.91)
Logical Memory Immediate Recall*	-0.17 (0.53)	0.55 (0.81)	0.58 (0.75)	0.20 (0.39)	-0.24 (0.52)	-1.60 (0.81)
Faces Delayed Recognition*	-0.60 (0.35)	0.43 (0.67)	1.37 (0.90)	-1.20 (0.48)	-0.73 (0.84)	-0.76 (0.96)

*Differences were significant between clusters, $p < .001$

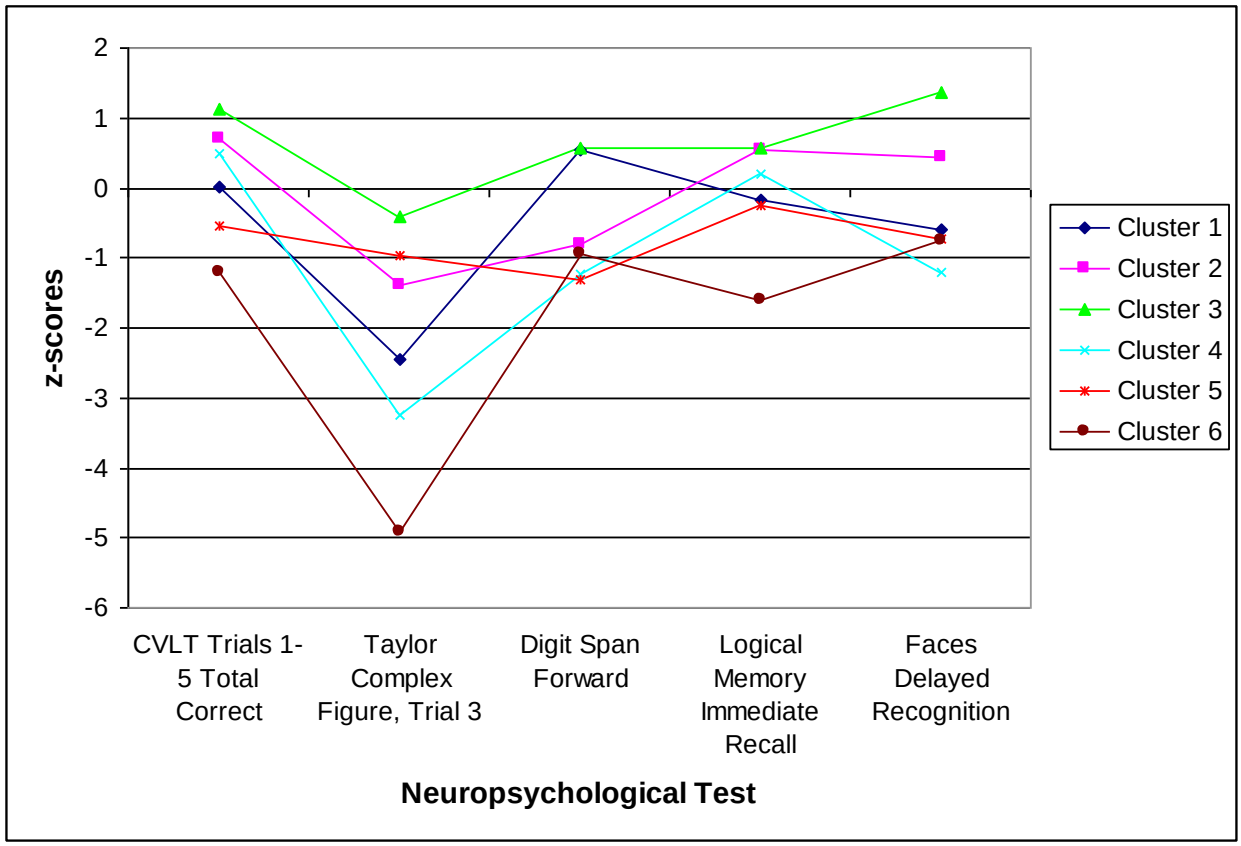

Figure 3. Performance of six clusters on classification variables.

Due to the small sample sizes in the 6-cluster solution, number of tests in the impaired range was collapsed into two levels for chi-square analyses. Level one consisted of patients with 0 or 1 test in the impaired range (*n* = 31). Level two consisted

of patients with 2 to 5 tests in the impaired range (n = 36). Pearson's chi-square analysis indicated that there was a significant relationship between cluster assignment and number of tests in the impaired range (χ^2 = 38.065, df = 5, p < .001). Inspection of the contingency tables showed that clusters 1, 2, and 3 had significantly more patients with 0 or 1 test in the impaired range than patients with 2 to 5 tests in the impaired range (see Table 12). In contrast, clusters 4, 5, and 6 had significantly more patients with 2 to 5 tests in the impaired range than patients with 0 or 1 test in the impaired range.

Table 12
Chi-Square Contingency Table: 6-Clusters by Level of Impairment

	0 or 1 impaired score	2 to 5 impaired scores	Total
Cluster 1	8	2	10
Cluster 2	11	3	14
Cluster 3	8	0	8
Cluster 4	2	8	10
Cluster 5	2	9	11
Cluster 6	0	14	14
Total	31	36	67

A one-way MANOVA was used to compare the six cluster groups on the five classification variables. A significant effect of group was obtained, F(25, 305) = 8.38, p < 0.001, Pillai's Trace = 2.046, partial eta squared = .407. Using a Bonferroni adjusted alpha level of 0.01, univariate effects were significant for all five classification variables (p < 0.001). Bonferroni post-hoc comparisons can be found in Appendix C.

With respect to demographic and seizure variables, there were significant differences in IQ scores for the six clusters, F(5, 61) = 12.56, p < .001. Bonferroni post-hoc comparisons can be found in Appendix D. In addition, there was a trend towards cluster 3 members having more years of education, F(5, 61) = 2.21, p = .06, than cluster

6. Means and standard deviations are presented in Table 13. The six clusters did not differ significantly in terms of age, duration of epilepsy, or age at onset of epilepsy. Chi-square analysis indicated no relationship between cluster assignment and sex.

Table 13
Six Cluster Demographic and Seizure Characteristics *M* (*SD*)

	Cluster 1 (*n* = 10)	Cluster 2 (*n* = 14)	Cluster 3 (*n* = 8)	Cluster 4 (*n* = 10)	Cluster 5 (*n* = 11)	Cluster 6 (*n* = 14)
Age	29.1 (9.32)	36.14 (13.03)	34.75 (10.42)	35.7 (7.39)	38.09 (13.72)	37.43 (13.53)
Sex (% male)	60	14	50	20	45	64
Years of Education	13.5 (2.37)	13.71 (1.86)	15.63 (2.00)	13.9 (2.03)	13.27 (1.74)	12.43 (2.90)
IQ*	99.40 (9.90)	105.00 (8.84)	110.00 (9.02)	91.50 (12.13)	88.73 (16.75)	75.64 (13.19)
Age at onset	15.52 (9.36)	16.78 (14.48)	16.02 (8.58)	16.57 (10.35)	15.99 (13.47)	16.83 (13.88)
Duration (years)	13.58 (12.35)	17.92 (16.25)	18.73 (11.39)	19.13 (10.59)	22.1 (16.84)	20.6 (13.43)

*Differences were significant between clusters, $p < .001$

Assessment of Internal and External Validity of Clusters

Volumetric Analysis of Clusters

MRI volumes for the six primary regions of interest (ROIs) and the fourteen ROI combinations (right plus left volumes, right minus left volumes, etc.) were compared for the cluster groups using one-way ANOVAs. When sample sizes allowed, one-way MANOVAs were used to compare the cluster groups on just the six primary regions of interest. Bonferroni post-hoc pairwise comparisons were used where applicable. All MRI volumes were multiplied by slice thickness to correct for differences in slice thickness (For comparison purposes, these analyses were repeated with MRI scans divided into two groups based on slice thickness. See Appendix A for the results of those analyses.)

For the 2-cluster solution, left hippocampal volumes were significantly greater, $F(1, 24) = 4.961$, $p = .036$, for patients in cluster 1 ($M = .3539$, $SD = .06$, $n = 15$) than

patients in cluster 2 (*M* = .3024, *SD* = .06, *n* = 11). However, this difference was not significant when a Bonferroni corrected *p* value of .0025 was applied. The two groups did not significantly differ on any other brain volume measures.

When a one-way MANOVA was used to compare MRI volumes for the two groups on just the six primary ROIs (i.e., volumes for the left and right hippocampus, left and right perirhinal cortex, and left and right anterior temporal lobe), no significant effect of group was obtained. Univariate tests indicated that left hippocampal volumes were significantly greater, $F(1, 23) = 4.692$, $p = .041$, for patients in cluster 1 than patients in cluster 2. However, this difference was not significant when a Bonferroni corrected *p* value of .008 was applied.

A one-way ANOVA for the 3-cluster solution indicated that patients in cluster 1 (*M* = .35, *SD* = .06, *n* = 14) had significantly higher, $F(2, 23) = 3.86$, $p = .036$, left hippocampal volumes than patients in cluster 3 (*M* = .27, *SD* = .05, *n* = 5;). In addition, patients in cluster 3 had significantly higher, $F(2, 23) = 4.02$, $p = .033$, right anterior temporal lobe volumes (*M* = 2.18, *SD* = .56, *n*= 5) than patients in cluster 2 (*M* = 1.51, *SD* = .11, *n* = 6). However, these differences were not significant when a Bonferroni corrected *p* value of .008 was applied.

For the 6-cluster solution, ANOVA was used to compare MRI volumes for only three clusters (clusters 1, 4, and 6) due to small sample sizes for the other clusters. Cluster 4 had significantly higher, $F(2, 15) = 4.62$, $p = .027$, left hippocampal volume (*M* = .37, *SD* = .05, *n* = 5) than cluster 6 (*M* = .27, *SD* = .06, *n* = 4). However, cluster 6 had significantly higher, $F(2, 14) = 4.27$, $p = .036$, right anterior temporal lobe volume (*M* =

2.37, *SD* = .43) than cluster 4 (*M* = 1.59, *SD* = .22). However, these differences were not significant when a Bonferroni corrected *p* value of .008 was applied.

Cluster Analysis of Alternative Classification Variables

Cluster analyses were repeated using the five second-highest loading test variables from the original principal components analysis. Using Ward's clustering method, 6 potential solutions were identified by examining the agglomeration schedule (cluster sizes 2, 3, 4, 6, 9, and 10).

After k-means iterative partitioning, cluster membership assignment using Ward's clustering method was compared on these alternative classification variables to membership assignment on the original classification variables. The 2-cluster solution had good concordance with 85% (*n* = 57) of patients being assigned to the same cluster. In contrast, only 60% of patients (*n* = 40) were assigned to the same cluster in the 3-cluster solution. Similarly, only 55% of patients (*n* = 37) were assigned to the same cluster for the 6-cluster solution.

Clinical Classifications Compared to Cluster Assignment

Neuropsychological classification of patients. Based on visual inspection of the 25 neuropsychological test scores used for the initial principal components analysis, patients were classified as having visuospatial deficits only (*n* = 21), verbal deficits only (*n* = 3), verbal and visuospatial deficits (*n* = 25), or no verbal or visuospatial deficits (*n* = 18). This classification of patients was based on clinical judgment rather than a formal algorithm. Generally, a patient was considered to have deficits if he/she obtained a norm-referenced z-score of -1.00 or less on one or more delayed recall variables, or -1.00 or less on more than one learning trial. However, the pattern of scores was also

considered. For example, a mildly impaired score on the first one or two learning trials was considered to reflect poor attention rather than poor memory when scores on subsequent trials were well within the average range. Thus, a patient with this pattern of performance would not be classified as having a memory impairment. Pearson's chi-square was used to assess whether this neuropsychological classification of patients was related to how patients were clustered using Ward's method (k-means refined). Due to the small number of patients classified as having only verbal deficits, these cases were not included in the analyses.

For the two-cluster solution, there was a significant relationship between this neuropsychological classification of patients and classification of patients using Ward's clustering method ($\chi^2 = 35.18$, $df = 2$, $p < 0.001$). Specifically, 24 out of 25 patients (96%) classified as having both verbal and visuospatial deficits were placed in cluster 2 using Ward's method (see Table 14). Seventeen out of eighteen patients (94.4%) classified as having no verbal or visuospatial deficits were placed in cluster 1 using Ward's method. Patients classified as having visuospatial deficits only, however, were evenly distributed between cluster 1 ($n = 11$) and cluster 2 ($n = 10$).

Table 14
Comparison of Ward's Method 2-Cluster Assignment With Neuropsychological Classification

Clinical classification	Cluster 1	Cluster 2	Total
visuospatial deficits	11	10	21
verbal and visuospatial deficits	1	24	25
no verbal or visuospatial deficits	17	1	18
verbal deficits	2	1	3
Total:	31	36	67

For the 3-cluster solution there was also a significant relationship between neuropsychological classification of patients and how patients were clustered using

Ward's method ($\chi^2 = 37.84$, $df = 4$, $p < 0.001$). Again, the relationship appeared to be driven primarily by the "verbal plus visuospatial deficits" group and the "no verbal or visuospatial deficits" group. Specifically, 17 out of the 25 patients classified as having both verbal and visuospatial deficits were placed in cluster 3; and 16 of the 18 patients classified as having no verbal or visuospatial deficits were placed in cluster 1 (see Table 15).

Table 15
Comparison of Ward's Method 3-Cluster Assignment With Neuropsychological Classification

Clinical classification	Cluster 1	Cluster 2	Cluster 3	Total
visuospatial deficits	9	8	4	21
verbal and visuospatial deficits	1	7	17	25
No verbal or visuospatial deficits	16	2	0	18
verbal deficits	2	0	1	3
Total:	28	17	22	67

The relationship between the neuropsychological classification of patients and how patients were clustered using Ward's method was also significant for the 6-cluster solution, ($\chi^2 = 43.18$, $df = 10$, $p < 0.001$). Inspection of the contingency table for the 6-cluster solution revealed that cluster 6 ($n = 14$) had a much higher number of patients with both verbal and visuospatial deficits ($n = 13$) than clusters 1 through 5 (see Table 16). Clusters 1, 4, and 5 had the second highest number of patients classified as having both verbal and visuospatial deficits, with 4 patients each. It is also significant to note that only one patient in cluster 6 was *not* classified as having both verbal and visuospatial deficits.

Table 16
Comparison of Ward's Method 6-Cluster Assignment with Neuropsychological Classification

Clinical classification	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Total
visuospatial deficits	3	6	1	6	4	1	21
verbal and visuospatial deficits	4	0	0	4	4	13	25
no verbal or visuospatial deficits	3	7	6	0	2	0	18
verbal deficits	0	1	1	0	1	0	3
Total:	10	14	8	10	11	14	67

Clinically classified patients were also compared on the five neuropsychological classification variables using one-way MANOVA. Due to the small sample size (n = 3), patients classified as having verbal deficits only were not included in this analysis. A significant effect of group was obtained, $F(10, 116) = 8.76$, $p < 0.001$, Pillai's Trace = 0.86, partial eta squared = .430. Using a Bonferroni adjusted alpha level of 0.01, univariate effects were significant for four of the five classification variables ($p < 0.001$, see Table 17).

Table 17
z-scores on Classification Variables for Neuropsychologically Classified Groups *M* (*SD*)

Test variable	Type of deficit(s)		
	Visuospatial (n= 21)	Verbal + Visuospatial (n = 25)	None (n = 18)
CVLT Trials 1-5 Total Correct*	0.45 (0.71)	-0.87 (0.65)	0.79 (0.53)
Taylor Complex Figure, Trial 3*	-2.52 (1.74)	-4.06 (2.24)	-0.29 (0.77)
Digit Span Forward	-0.81 (0.83)	-0.84 (0.95)	-0.14 (0.93)
Logical Memory Immediate Recall*	0.11 (0.79)	-0.95 (0.98)	0.61 (0.53)
Faces Delayed Recognition*	-0.49 (0.98)	-0.85 (0.78)	0.50 (1.04)

Differences were significant between groups, $p < 0.001$

Patients clinically classified as having visuospatial deficits only had significantly higher scores on the CVLT Trials 1-5 Total, the Logical Memory Immediate Recall, and the Taylor Figure 3rd Recall variables compared to patients classified as having both verbal and visuospatial deficits. However, they had significantly lower scores on the

Taylor Figure 3rd Recall and the Faces Delayed Recognition variables than patients classified as having no deficits.

Patients clinically classified as having both verbal and visuospatial deficits scored significantly lower on the CVLT Trials 1-5 Total, the Logical Memory Immediate Recall, and the Taylor Figure 3rd Recall variables than patients classified as having visuospatial deficits only and patients classified as having no deficits. They scored lower than patients classified as having no deficits on the Faces Delayed Recognition. There was also a trend toward these patients scoring lower on the Digit Span Forward variable than patients classified as having no deficits (the difference was significant if a Bonferroni correction was not applied). These groups did not differ significantly on demographic (age, sex) or seizure characteristic variables (age at onset, duration of epilepsy).

Volumetric analysis of neuropsychologically classified groups. Brain volumes were compared for patients who were clinically classified as having visuospatial deficits only (n = 7), verbal plus visuospatial deficits (n = 10), or no verbal or visuospatial deficits (n = 8). All MRI volumes were multiplied by slice thickness to correct for differences in slice thickness (For comparison purposes, these analyses were repeated with MRI scans divided into two groups based on slice thickness. See Appendix E for the results of those analyses.). Due to the small number of patients classified as having verbal deficits only (n = 1), this group was not included in these analyses. Brain volumes for the three groups were analyzed using one-way ANOVA with Bonferroni post-hoc pairwise comparisons. Patients classified as having both verbal and visuospatial deficits (M = .29, SD = .06) had significantly lower, $F(2, 22)$ =

4.50, p = .023, left hippocampal volumes than patients classified as having neither verbal nor visuospatial deficits (M = .36, SD = .05). However, this difference was not significant when a Bonferroni corrected p value of .0025 was applied. In addition, there was a trend towards patients with both verbal and visuospatial deficits (M = .05, SD = .08) having a greater discrepancy, F (2, 22) = 3.40, p = .052, between right and left hippocampal volumes (right volume minus left volume) than patients with no verbal or visuospatial deficits (M = -0.03, SD = .05). There were no other significant differences in brain volume for the three groups.

When a one-way MANOVA was used to compare MRI volumes for the three groups on just the six regions of interest (i.e., volumes for the left and right hippocampus, left and right perirhinal cortex, and left and right anterior temporal lobe), no significant effect of group was obtained. Univariate tests indicated that left hippocampal volumes were significantly smaller, F (2, 21) = 4.327, p = .027, for patients classified as having both verbal and visuospatial deficits than for patients classified as having neither verbal nor visuospatial deficits. However, this difference was not significant when a Bonferroni corrected p value of .008 was applied.

Neuroradiological classification of patients. External validity of cluster assignment was also assessed by sorting patients based on independent neurologists' and/or radiologists' localization interpretations of EEG and/or neuroimaging results and comparing the neuroradiological classification to classification based on Ward's method. Four groups were obtained based on neuroradiological classification: 1) right temporal lobe dysfunction (n = 23), 2) left temporal lobe dysfunction (n = 23), 3) bilateral temporal

lobe dysfunction (*n* = 10), and no temporal lobe dysfunction (*n* = 11). More specific localization information was not available.

For the two-cluster solution, Pearson's chi-square test indicated there was no significant relationship between the neuroradiological classification of patients and how patients were clustered using Ward's method. However, inspection of the contingency table revealed that 8 out of 10 patients classified as having bilateral temporal lobe involvement were placed in cluster 2 using Ward's method; and 8 out of 11 patients classified as having no temporal lobe dysfunction were placed in cluster 1 (see Table 18). Patients classified as having either right or left temporal lobe dysfunction were more evenly distributed between the two clusters.

Table 18
Comparison of Ward's Method 2-Cluster Assignment With Neuroradiological Classification

Neuroradiological classification	Cluster 1	Cluster 2	Total
Right temporal dysfunction	12	11	23
Left temporal dysfunction	9	14	23
Bilateral temporal dysfunction	2	8	10
No identified area of dysfunction	8	3	11
Total:	31	36	67

For the three-cluster solution, there was a significant relationship between neuroradiological classification of patients and cluster assignment using Ward's method ($\chi^2 = 14.42$, $df = 6$, $p = 0.03$). Inspection of the contingency table (see Table 19) revealed that 20 of the 23 patients classified as having right temporal dysfunction were concentrated in clusters 1 (*n* = 10) and cluster 2 (*n* = 10). Similarly, 20 of the 23 patients classified as having left temporal dysfunction were concentrated in cluster 1 (*n* = 9) and cluster 2 (*n* = 11). Six of the 10 patients classified as having bilateral damage were

concentrated in cluster 3; and 7 of the 11 patients classified as having no temporal dysfunction were concentrated in cluster 1.

Table 19
Comparison of Ward's Method 3-Cluster Assignment With Neuroradiological Classification

Physicians' classifications	Cluster 1	Cluster 2	Cluster 3	Total
Right temporal dysfunction	10	10	3	23
Left temporal dysfunction	9	3	11	23
Bilateral temporal dysfunction	2	2	6	10
No identified area of dysfunction	7	2	2	11
Total:	28	17	22	67

For the 6-cluster solution, there was also a significant relationship between neuroradiological classification of patients and cluster assignment using Ward's method ($\chi^2 = 32.84$, $df = 15$, $p = 0.005$). Analysis of the contingency table, revealed that 14 of the 23 patients classified as having left temporal lobe damage or dysfunction were concentrated in clusters 2 and 6; and 5 of the 11 patients having no identified area of damage or dysfunction were placed in cluster 3 (see Table 20).

Table 20
Comparison of Ward's Method 6-Cluster Assignment With Neuroradiological Classification

	Presence of Temporal Lobe Damage				
	Right	Left	Bilateral	None	Total
Cluster 1	6	4	0	0	10
Cluster 2	4	6	2	2	14
Cluster 3	2	1	0	5	8
Cluster 4	6	2	1	1	10
Cluster 5	5	2	3	1	11
Cluster 6	0	8	4	2	14
Total:	23	23	10	11	67

Patients classified by the presence or absence of temporal lobe damage/dysfunction were also compared on the five neuropsychological classification variables using one-way MANOVA. A significant effect of group was obtained, $F(15, 183) = 2.447$, $p = 0.003$, Pillai's Trace = 0.501, partial eta squared = .167. Using a

Bonferroni adjusted alpha level of 0.01, univariate effects were significant for two of the five classification variables (CVLT Trials 1-5 Total and Logical Memory Immediate Recall). Group means and standard deviations can be found in Table 21.

Table 21
z-Scores on Classification Variables for Groups Classified by EEG/Imaging *M* (*SD*)

Test variable	Presence of temporal lobe damage/dysfunction			
	Left (*n* = 23)	Right (*n*= 23)	Bilateral (*n* = 10)	None (*n* = 11)
CVLT Trials 1-5 Total*	-0.25 (1.06)	0.37 (0.62)	-0.72 (0.81)	0.50 (1.07)
Taylor Figure, Trial 3	-2.99 (2.12)	-1.80 (1.92)	-2.56 (2.71)	-2.13 (3.11)
Digit Span Forward	-0.66 (0.97)	-0.65 (1.10)	-0.75 (0.56)	-0.32 (0.91)
Logical Memory Imm. Recall*	-0.39 (1.09)	0.09 (0.51)	-1.17 (0.89)	0.58 (1.08)
Faces Delayed Recognition	-0.41 (0.93)	-0.54 (1.01)	-0.37 (1.19)	0.51 (1.20)

Differences were significant between groups, $p < .01$

Specifically, patients classified as having left temporal lobe damage/dysfunction scored significantly lower on the Logical Memory Immediate Recall variable than patients classified as having no temporal lobe damage/dysfunction. Patients classified as having right temporal lobe damage/dysfunction scored significantly higher on the CVLT Trials 1-5 Total and the Logical Memory Immediate Recall variables than patients classified as having bilateral temporal lobe damage/dysfunction. There was a trend toward these patients scoring significantly lower on the Faces Delayed Recognition variable than patients classified as having no temporal lobe damage/dysfunction. Finally, patients classified as having bilateral temporal lobe damage/dysfunction scored significantly lower on the CVLT Trials 1-5 Total and the Logical Memory Immediate Recall variables than patients classified as having no temporal lobe damage/dysfunction. The groups did not differ significantly on demographic (age, sex) or seizure characteristic variables (age at onset, duration of epilepsy).

Volumetric analysis of neuroradiologically classified patients. One-way ANOVA's were also used to compare MRI volumes of patients grouped by area of cortical damage or dysfunction based on EEG and/or neuroimaging. All MRI volumes were multiplied by slice thickness to correct for differences in slice thickness. (For comparison purposes, these analyses were repeated with MRI scans divided into two groups based on slice thickness. See Appendix F for the results of those analyses.) No significant differences in brain volumes were found for patients diagnosed with left temporal lobe damage or dysfunction (n = 13; including patients diagnosed with bilateral temporal lobe damage) compared to patients not diagnosed with left temporal lobe damage or dysfunction (n = 13; including patients with no identified area of damage or dysfunction). Nor were there any significant differences between patients diagnosed with right temporal lobe damage or dysfunction (including patients diagnosed with bilateral damage or dysfunction) compared to patients not diagnosed with right temporal lobe damage or dysfunction (including patients with no identified area of damage or dysfunction). Likewise, no significant differences in brain volumes were found when patients were separated into four groups based on area of damage or dysfunction (left temporal, n = 8; right temporal, n = 8; bilateral, n = 5; and no identified area of damage or dysfunction, n = 5).

Discussion

There is strong evidence in the literature to support the existence of memory impairments in patients with temporal lobe epilepsy (TLE). This is not surprising given the fact that the temporal lobe brain structures involved in TLE play a central role in consolidating information into memory. It is widely accepted that patients whose seizure focus is in the left temporal lobe (LTLE) tend to have verbal memory impairments, whereas patients whose seizure focus is in the right temporal lobe (RTLE) tend to have visuospatial memory impairments (though there are many exceptions to this rule). However, in both the animal and human literature, there is evidence of functional subdivisions *within* the left and right temporal lobes such that different brain structures are important for different types of verbal and visuospatial memory. Thus, it is reasonable to expect that more specific subtypes of memory impairment may exist in TLE based on differences in seizure foci within the left and right temporal lobes. In addition, variables such as age at onset of seizures, duration of seizure disorder (time since diagnosis), educational level, and sex have been associated with different patterns of memory performance in patients with TLE. The aim of the present study was to identify more specific subtypes of memory-impairments in patients with TLE using a variety of different neuropsychological measures of memory functioning and quantitative cluster analytic methods. Such an improved and more specific TLE classification system could have prognostic significance for patients and could contribute to our knowledge about the organization of memory systems of the human brain.

Based on a review of the literature, it was hypothesized that 5 memory-based subtypes would emerge from the cluster analyses. The hypothesized subtypes consisted of: 1) patients with isolated verbal episodic memory deficits, 2) patients with both verbal episodic and verbal semantic memory deficits, 3) patients with isolated deficits in figural episodic memory and spatial memory, 4) patients with global visuospatial memory deficits (figural episodic, spatial, and face recognition), and 5) patients with global verbal and visuospatial memory deficits. However, the cluster analyses resulted in three different potential classification solutions, consisting of 2, 3, and 6-clusters (i.e., memory subtypes).

Across all three cluster solutions, a total of four memory subtypes were identified in this sample: 1) patients with mild to moderate figural memory deficits; 2) patients with moderate to severe figural memory deficits, mild facial recognition deficits, and mild attention/concentration deficits; 3) patients with severe figural memory deficits and mild verbal episodic memory deficits; and 4) patients with no episodic or semantic memory deficits. The three clustering solutions are described in more detail below.

Two-Cluster Solution

In the two cluster solution, patients appeared to be clustered into a higher functioning group (cluster 1) and a lower functioning group (cluster 2). Though both cluster means were in the impaired range relative to normative data on a test of visuospatial memory (the Taylor Complex Figure 3rd recall variable), the cluster 1 mean was only in the mildly impaired range, whereas the cluster 2 mean was in the severely impaired range. On the other 4 neuropsychological classification variables, means for both clusters were in the normal range; however, cluster 1 consistently performed 1 or

more standard deviations above cluster 2. In addition, inspection of the individual patient profiles revealed that patients who had no test scores in the impaired range were placed exclusively in cluster 1. In contrast, 24 out of 25 patients with impaired scores on at least 3 of the classification variables were placed in cluster 2.

The external validity of these clusters was supported by the finding that patients in the higher-performing cluster 1 had significantly more years of education than patients in the lower-performing cluster 2. In addition, independent neuropsychological classification of patients also differed for the two groups as would be expected. Specifically, individuals in cluster 1 were statistically more likely to be classified as having no verbal or visuospatial deficits. In contrast, individuals in cluster 2 were statistically more likely to be classified as having both verbal and visuospatial deficits. When classified based on neuroradiological data, there was a trend toward patients in cluster 1 being classified as having no identifiable temporal lobe damage or dysfunction, whereas there was a trend for patients in cluster 2 to be classified as having bilateral temporal lobe damage or dysfunction.

On demographic variables, cluster 2 had a significantly higher percentage of males than females. The two clusters did not differ significantly differ in terms of age, duration of illness, or age at onset of illness. Contrary to expectation, the two clusters did not show any significant differences in temporal lobe brain volumes, though there was a trend towards higher left hippocampal volumes in cluster 1.

Three-Cluster Solution

In the three-cluster solution, patients generally appeared to be clustered into mildly impaired (cluster 1), moderately impaired (cluster 2), and more severely impaired

(cluster 3) groups. However, these groups do not appear to simply represent a continuum of severity of memory impairment because the *pattern* of memory impairment was different for the three groups. Cluster 1 exhibited only mild deficits in visuospatial memory. Cluster 2 exhibited moderate deficits in visuospatial memory plus mild deficits in both short-term memory/attention (Digit Span forward) and delayed facial recognition. And cluster 3 exhibited severe deficits in visuospatial memory, plus mild deficits in verbal memory (Logical Memory Immediate Recall and CVLT Trials 1-5 Total Correct). Inspection of the individual patient profiles revealed that all 15 patients who had no test scores in the impaired range were placed in cluster 1. In contrast, 16 out of 25 patients with impaired scores on at least 3 of the classification variables were placed in cluster 3 (the remaining 9 cases were placed in cluster 2).

The external validity of these clusters was supported by the finding that patients in the highest-performing cluster 1 had significantly more years of education than patients in the lowest-performing cluster 3. Independent neuropsychological classification of patients also differed for the three groups as would be expected. Specifically, 68% of the patients classified as having both verbal and visuospatial deficits were placed in cluster 3; and 89% of the patients classified as having no verbal or visuospatial deficits were placed in cluster 1. There was also a significant relationship between neuroradiological classification of patients and cluster assignment using Ward's method. Specifically, 64% of the patients classified as having no temporal dysfunction were concentrated in cluster 1. Sixty percent of the patients classified as having bilateral damage were concentrated in cluster 3. Cluster 3 had a significantly

higher percentage of males than females. However, the three clusters did not differ significantly differ in terms of age, duration of illness, or age at onset of illness.

Contrary to expectation, differences in brain volumes for the three clusters did not continue to reach significance when a Bonferroni correction was applied. However, there was a trend towards cluster 1 patients having higher left hippocampal volumes than patients in cluster 3. This might be related to the fact that verbal memory deficits were found in cluster 3, but not cluster 1. Similarly, there was a trend towards patients in cluster 3 having higher right anterior temporal lobe volumes than patients in cluster 2. This might be related to the fact that visuospatial memory deficits were limited to figural memory in cluster 3, but included both figural and facial recognition deficits in cluster 2.

These results are consistent with Hermann et al. (2007) who reported obtaining a 3-cluster solution in a group of patients with TLE. Though Hermann et al. examined patients' performance on a number of different cognitive variables in addition to memory (e.g., executive functioning, processing speed, and language), the 3 groups obtained in that study were also generally described as having mild, moderate, and severe memory impairment. Also consistent with Hermann et al., the three clusters obtained in this study showed different patterns of impairment on the classification variables. This suggests that the clusters obtained in both studies do not merely represent a continuum of severity of cognitive impairment.

Six-Cluster Solution

The six-cluster solution most closely corresponds, at least in terms of the number of clusters, to the five memory subtypes that were hypothesized at the beginning of this study. In addition, the expected patterns of memory impairment were found in a few,

but not all, of these clusters. Reviewing the original study hypotheses in order: Hypothesis 1 stated that a cluster would emerge with “isolated verbal episodic memory deficits, which may be related to restricted lesions of the left hippocampus and later seizure onset.” Similarly, hypothesis 2 stated that a cluster would emerge with “both verbal episodic and verbal semantic memory deficits due to more widespread left temporal lesions including perirhinal and anterior temporal pole regions.” Contrary to expectation, none of the six clusters demonstrated isolated verbal episodic memory deficits.

The failure to identify a subgroup of TLE patients with isolated verbal memory deficits is consistent with other published studies, which demonstrate that even patients with verified left temporal lobe epilepsy show deficits in both verbal and visuospatial memory tasks (Wilde et al., 2001). This might account for a discrepancy that was found in the present study between neuropsychological classification of patients and neuroradiological classification of patients. Specifically, *half* of the patients classified as having isolated left temporal lobe damage or dysfunction based on neuroradiological data, were classified as having both verbal and visuospatial deficits based on neuropsychological test scores. If left hemisphere brain structures are more important for verbal memory and right hemisphere structures more important for visuospatial memory, patients with isolated left temporal lobe damage or dysfunction should have isolated verbal memory deficits. One explanation for the unexpected verbal plus visuospatial deficits is that verbal strategies may have been used to encode the visuospatial stimuli used in this study (Jambaqué, 1993; Nolan, 2004), thereby putting patients with verbal memory impairment at a broader cognitive disadvantage. Another

explanation for this finding is that visuospatial memory may have more widespread or bilateral representation in the brain (Alessio et al., 2004).

Hypothesis 3 stated that a cluster would emerge with “deficits in figural episodic memory and spatial memory, which may be due to restricted right hippocampal lesions and later seizure onset.” Spatial memory could not be assessed due to the lack of a valid measure in the available assessment battery; however, two clusters were found which exhibited isolated figural episodic memory deficits (clusters 1 and 2). Contrary to expectation, these clusters did not appear to exhibit the isolated right hemisphere damage/dysfunction that was predicted. Based on neuroradiological classification, only 60% of patients in cluster 1 were classified as having isolated right temporal lobe damage or dysfunction. The remaining 40% were classified as having isolated left temporal lobe damage. In cluster 2, 29% of patients were classified as having isolated right temporal lobe damage and 43% were classified as having isolated left temporal lobe damage or dysfunction.

Isolated visuospatial deficits have been reported in patients with isolated left temporal lobe damage or dysfunction (Gleissner, Helmstaedter, and Elger, 2002). However, these deficits have been associated with early onset of seizures and attributed to functional reorganization of the brain. This could not account for the findings in the present study where the 6 clusters did not differ significantly in terms of age at onset, and only two of the ten patients classified as having isolated left temporal lobe damage or dysfunction had onset of their seizure disorder before age 14.

Hypothesis 4 predicted the emergence of a cluster with “global visuospatial memory deficits (figural episodic, spatial, and face recognition), which may be related to

more widespread right temporal involvement including the hippocampus, perirhinal cortex, and anterior temporal pole." Patients in cluster 4 most closely correspond to this hypothesis, exhibiting severe deficits in visuospatial memory and mild deficits in facial recognition. In addition, there was a trend towards patients in cluster 4 having lower right anterior temporal lobe volumes than patients in cluster 6. This might account for the impairment in facial recognition that was found in cluster 4 but not cluster 6.

Contrary to expectation, however, only 6 of the 10 patients in cluster 4 were classified based on neuroradiological data as having isolated right temporal lobe damage or dysfunction. As for the remaining four patients, two were classified as having isolated left temporal lobe damage, one was classified as having bilateral temporal damage, and one was classified as having no temporal lobe damage or dysfunction. It is hard to account for the isolated visuospatial deficits in the two patients with isolated left temporal lobe damage. These patients did not have onset of their seizure disorders at an early age, so functional reorganization is unlikely. As for the patient with no identified temporal lobe damage or dysfunction, there was evidence of bilateral frontal lobe damage or dysfunction which may have accounted for her impaired performance. Specifically, it has been found that performance on complex figure memory tasks is positively correlated with organizational skills, which are believed to depend upon the frontal lobes (Newman & Krikorian, 2001).

Hypothesis 5 predicted the emergence of a cluster with "global verbal and visuospatial memory deficits, which may be related to earlier seizure-onset and bilateral temporal lobe lesions." Cluster 6 most closely resembles this pattern of impairment on neuropsychological tests with mild impairment on verbal memory tasks and severe

impairment on a task of visuospatial memory. As would be expected there was a trend for this cluster to have lower left hippocampal volumes than cluster 4 which did not exhibit verbal memory impairment, and higher right anterior temporal lobe volumes than cluster 4 which exhibited impairment in facial recognition memory. Furthermore, 13 of the 14 patients in this cluster were independently classified as having both verbal and visuospatial memory deficits based on neuropsychological data.

However, contrary to the initial hypothesis, 8 of the 14 patients in this cluster were independently classified based on neuroradiological data as having isolated left temporal lobe damage or dysfunction. This is consistent with some studies in which impairment in visuospatial tasks has been reported in patients with unilateral LTLE. For example, Glikmann-Johnston et al. (2008) found that both right and left TLE patients performed significantly worse than controls on three different spatial memory tasks assessed via a virtual-reality paradigm.

The failure to find the expected bilateral temporal lobe dysfunction in these patients with both verbal and visuospatial memory deficits might be attributable to insensitivity of current imaging methods. According to Squire and Zola (1998, p. 210) “Even high resolution MRI cannot detect cell loss that is easily detected in histological examinations.” It is also possible that the theory on which this study’s hypotheses are based, namely that left temporal structures are important for verbal memory and right temporal structures are important for visuospatial memory, is not accurate or is accurate only under certain circumstances. This would account for the large number of published studies which failed to demonstrate verbal and visuospatial memory impairments in patients with LTLE and RTLE, respectively.

Two unexpected clusters emerged in the 6-cluster solution. The first, cluster 3, exhibited no deficits on any of the neuropsychological classification variables. Congruently, 5 of the 11 patients classified as having no identified area of brain damage or dysfunction based on neuroradiological data were placed in cluster 3. In addition, 6 of the 8 patients in this cluster were independently classified as having neither verbal nor visuospatial deficits based on neuropsychological data. With respect to demographic variables, there was a trend towards the unimpaired cluster 3 members having more years of education than the most impaired cluster 6.

Although the identification of an unimpaired cluster was not predicted, in retrospect, it is not surprising that such a group was identified. When analyzed as a group, TLE patients frequently demonstrate memory impairments. However, at the individual level, not all patients demonstrate these deficits. Typically, these findings are not discussed in the literature, where the focus is on group-level differences. For example, in a sample of patients with left or right hippocampal atrophy described by Alessio et al. (2006) 11 of their 39 patients exhibited no impairments on measures of general memory, verbal memory, and visuospatial memory. This finding was not mentioned in the text, but was embedded in a table of individual test scores. The lack of memory impairments in some patients may be due to a number of factors, including different etiologies, differences in seizure foci, lower frequency of seizures, and combination of anti-epileptic drugs used.

The second unexpected cluster, cluster 5, exhibited isolated mild deficits on Digit Span Forward despite the fact that all but one patient was classified as having some form of temporal lobe damage or dysfunction based on neuroradiological classification.

Typically, patients with TLE have preserved short term memory; and even patients with large mesial temporal lobe lesions perform within normal limits on the Digit Span subtest (Squire et al., 2004). It may be that the discrepant findings in the present study are due to differences in temporal lobe seizure foci. For example, perhaps the temporal lobe damage/dysfunction in these individuals was limited to more anterior and lateral temporal structures, whereas mesial temporal lobe structures important for memory may have been spared. However, this hypothesis could not be confirmed as more specific localization information was not available for these patients.

In summary, three potential clustering solutions were identified in this sample. In a two cluster solution, patients appeared to be classified into higher-functioning and lower-functioning groups. In a three-cluster solution, different subtypes of memory impairment began to emerge. The three subtypes in this solution consisted of: 1) patients with mild figural memory deficits, 2) patients with moderate figural memory deficits, mild facial recognition deficits, and impaired attention/concentration, and 3) patients with severe figural memory deficits plus verbal episodic memory deficits. In a six-cluster solution, the same subtypes of memory impairment were found, except that there were two clusters with isolated figural memory deficits (one cluster had mild deficits, the other had moderate deficits). In addition two clusters emerged with no episodic or semantic memory deficits (one cluster exhibited isolated deficits in short term memory/attention, the other cluster performed within normal limits on all classification variables).

Contrary to expectation, the clusters found in this study did not exhibit the expected pattern of memory lateralization. Specifically, patients in clusters with isolated

visuospatial memory impairments were not significantly more likely to be classified as having isolated right temporal lobe damage or dysfunction based on neuroradiological data. In addition, no clusters emerged with isolated verbal memory impairments, despite the fact that twenty patients were classified as having isolated left temporal lobe damage or dysfunction based on neuroradiological data. On an individual level, only one of the twenty patients classified as having isolated left temporal lobe damage or dysfunction based on neuroradiological data showed the expected pattern of isolated verbal memory impairment. Only 9 of 22 patients classified as having isolated right temporal lobe damage or dysfunction showed the expected pattern of isolated visuospatial memory impairments. These findings call into question the theory that left temporal lobe structures are specialized for verbal memory whereas right temporal lobe structures are specialized for visuospatial memory.

It still remains to be determined whether different temporal lobe structures are important for different aspects of verbal and visuospatial memory. In the present study, MRI data were not available for many patients. This limited the ability to correlate differences in neuropsychological test performance with differences in brain volume. However, consistent with the literature, there was a trend towards some clusters with better verbal memory having higher left hippocampal volumes than clusters with poorer verbal memory. In addition, a trend towards higher anterior temporal lobe volumes was found in one cluster with circumscribed figural memory deficits compared to a cluster with both figural memory deficits and facial recognition deficits, as would be expected based on a review of the literature.

Although MRI was the imaging technique available for this study, the number of patients without any clear evidence of lesions, and its inconsistent mapping onto the subtypes raises the question whether it was an adequate method for subtype validation. Though improvements in MRI technology over the last decade have enabled the detection of even tiny epileptogenic lesions, these techniques still fail to identify any lesions in approximately 20% of patients (Siegel, 2004). It has been suggested that other physiological measures may be more sensitive to memory functions than MRI volumetry. For example, there is evidence that PET is a more sensitive interictal imaging technique than MRI. Though at least 30% of TLE patients have no evidence of hippocampal sclerosis on MRI, many of these patients have prominent focal or regional hypometabolism on PET scans (Carne et al., 2004). Another method which may be useful in epilepsy research, magnetic resonance spectroscopy (MRS), has been shown to be more sensitive to neurocognitive function than MRI in early stage Alzheimer's disease (Shiino, et al., 1993) and HIV (Meyerhoff, 1993). In a sample of TLE patients, Sawrie, Martin, Knowlton et al. (2001) found a relationship between verbal memory and magnetic resonance spectroscopy (MRS), but not MRI. Thus, for future studies the use of imaging methods other than MRI should be considered.

Future validation studies will also be needed to determine whether patients within different subtypes of memory impairment have different cognitive courses, or prognoses. Although the present study did not look at cognitive course as a function of group membership, Herman et al. (2007) found that patients with epilepsy had a poorer cognitive course than controls across all cognitive domains over a 4-year period, and

that lower-functioning clusters had a poorer cognitive course than higher-functioning clusters.

Ultimately, it also remains to be determined whether treatment outcomes differ for patients depending upon their pattern of memory impairment. It is already known that patients who have higher preoperative verbal memory have a higher risk for postoperative memory decline following left temporal lobectomy (Chelune et al., 1991). It is also possible that treatment outcomes differ for patients who represent different subtypes on verbal or visuospatial memory tests. Such information would be valuable for clinical decision making.

This study is unique in that, to the author's knowledge, only one other study (Hermann et al., 2007) has been published using cluster analytic methods to classify epilepsy patients based on their cognitive profiles. In that study, indices for a number of different cognitive domains were examined; and verbal and visuospatial memory tasks were collapsed into an "immediate memory" index score and a "delayed memory" index score. In contrast, in the present study, patients were classified based on their profiles on a variety of different verbal and visuospatial memory tasks. This enabled more specific subtypes of memory impairment to be identified.

Another unique feature of this study was that it compared three different classification systems: 1) cluster analysis, 2) clinical classification based on neuropsychological test scores, and 3) clinical classification based on neuroradiological data. Overall, both clinical classification methods showed good concordance with classification based on cluster analysis, although concordance for some clusters was much better than others. Concordance between cluster analysis and

neuropsychological classification appeared to be highest in patients classified as having both verbal and visuospatial deficits and in patients classified as having no deficits. Concordance between neuroradiological classification and cluster analysis appeared to be highest in patients classified as having bilateral temporal lobe damage/dysfunction and in patients classified as having no temporal lobe damage/dysfunction.

Several factors which may have impacted the results of this study should be mentioned. First, because this study was based in retrospective chart review, the neuropsychological measures used for cluster analyses were limited to those administered as part of a standard test battery. As a consequence, spatial memory could not be adequately assessed in this sample. Though the Spatial Span subtest of the WMS-III was conceptualized as a measure of spatial memory for the purposes of this study, it loaded on what appeared to be a short term memory/attentional component in an initial principal components analysis. The two highest-loading tests on that component were Digit Span Forward and Digit Span Backward.

Second, small sample sizes resulted in the violation of assumptions for some statistical analyses and, more importantly, may have limited power when the 6-cluster solution was evaluated. Small sample sizes also made it necessary to use multiple one-way ANOVAs, rather than MANOVAs for many of the analyses. Because of the large number of comparisons that were made, Bonferroni corrections were used. While this greatly reduces the likelihood of Type I errors, it could be argued that these corrections were overly conservative and may have resulted in some actual differences being missed.

Third, the sample in this study consisted of patients with intractable epilepsy. As patients with intractable seizures only represent 20% of the epilepsy population, these findings may not generalize to the remaining 80% of the population whose seizures are well-controlled. In addition, the small sample sizes in this study may have resulted in a biased sample, which limits its representativeness to patients with TLE. Patients with TLE are a heterogeneous group due to differences in seizure etiology (e.g., malformations, tumors, and traumatic brain injury), seizure frequency, seizure severity, and age at onset. The current sample may have had unique characteristics compared to those found in previous studies. Thus, with larger sample sizes, it is plausible that additional subtypes of memory impairment in TLE may be found, or the characteristics of the subtypes found may become clearer in some instances.

Even with those limitations, the results of this study support the hypothesis that subtypes of memory impairment *do* exist in patients with temporal lobe epilepsy. Some of these subtypes showed the expected localized differences in brain volume or trends towards expected differences; however, small sample sizes limited the ability to clearly validate all of their differences. It is conceivable that additional subtypes of memory impairment may be identified in future studies, particularly with larger sample sizes and with the inclusion of better measures of spatial memory.

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Appendix A: Volumetric analysis of clusters

(MRI scans divided into two groups based on slice thickness)

As a measure of external validity, MRI volumes for the six primary regions of interest (ROIs) and the fourteen ROI combinations (right plus left volumes, right minus left volumes, etc.) were compared for the cluster groups using one-way ANOVAs. When sample sizes allowed, MRI volumes for just the six primary regions of interest were compared for the cluster groups using one-way MANOVA. Bonferroni post-hoc pairwise comparisons were used where applicable. All scans were divided into two groups for volumetric analysis. The first group consisted of scans with slice thicknesses between 1.25 mm and 1.5 mm ("slicegroup 2;" n = 11). The second group consisted of: 1) scans with 1.0 mm slice thicknesses in which every other slice was measured, and 2) scans with 2.0 mm slice thicknesses ("slicegroup 1;" n = 15). The results of these analyses are found below.

"Slicegroup 1" (1mm and 2mm MRI Scans Only)

For the 2-cluster solution, patients in cluster 2 (n = 6) had significantly higher, $F(1, 13) = 5.01$, $p = .043$, left perirhinal volumes ($M = .12$, $SD = .02$) than patients in cluster 1 ($M = .09$, $SD = .03$, $n = 9$). However, this difference was not significant when a Bonferroni corrected p value of .0025 was applied. The two groups did not significantly differ on any other brain volume measures.

Similarly, when a one-way MANOVA was used to compare MRI volumes for the two clusters on just the six primary regions of interest (i.e., volumes for the left and right hippocampus, left and right perirhinal cortex, and left and right anterior temporal lobe)

no significant effect of group was obtained and univariate tests were not significant when a Bonferroni corrected *p* value of .008 was applied.

A one-way ANOVA for the 3-cluster solution, showed that the clusters differed significantly on two of the MRI variables. Specifically, patients cluster 1 had significantly higher, $F(2, 11) = 7.30$, $p = .010$, right anterior temporal lobe volumes ($M = .92$, $SD = .21$, $n = 6$) than patients in cluster 2 ($M = .79$, $SD = .03$, $n = 5$). Patients in cluster 3 had a significantly higher, $F(2, 11) = 6.26$, $p = .015$, combined right hippocampal, perirhinal, and anterior temporal lobe volume ($M = 1.61$, $SD = .13$) than patients in cluster 1 ($M = 1.21$, $SD = .22$) and patients in cluster 2 ($M = 1.12$, $SD = .11$). However, these differences were no longer significant after a Bonferroni corrected *p* value of .0025 was applied. MANOVA could not be performed for the 3-cluster solution due to small sample size. In addition, volumetric analysis by cluster was not performed for the 6-cluster solution due to small sample size.

"Slicegroup 2" (1.25 – 1.5 mm MRI Scans Only)

One-way ANOVAs were used to compare patients in the 1.25 – 1.5 mm MRI slice thickness group (slicegroup 2) on the MRI variables. For the 2-cluster solution, patients differed significantly on one of the MRI variables. Specifically, cluster 1 had significantly higher, $F(1, 9) = 5.135$, $p = .05$, right anterior temporal lobe volumes ($M = 1.42$, $SD = .27$, $n = 6$) than cluster 2 ($M = 1.12$, $SD = .09$, $n = 5$). However, this difference was no longer significant after a Bonferroni corrected *p* value of .0025 was applied. For the 3-cluster solution, there were no significant differences in brain volume; however, samples sizes were small and disparate (2, 3, and 6). Volumetric analysis by cluster was not performed for the 6-cluster solution due to small sample size.

Appendix B: Bonferroni Post-Hoc Comparisons: Significant Group Differences on Classification Variables for the Three-Cluster Solution

Dependent Variable	(I) Wards3R	(J) Wards3R	Mean Difference (I-J)	Std. Error	Sig.
CVLT Trials 1-5	1	2*	0.80492	0.17855	0.001
		3*	1.82936	0.16545	0.001
	2	3*	1.02444	0.18753	0.001
Digit Span forward	1	2*	1.35540	0.24404	0.001
	2	3*	-0.86647	0.25630	0.004
Taylor 3rd recall	1	3*	3.02154	0.56061	0.001
	2	3*	1.80135	0.63542	0.018
Logical Memory	1	3*	1.69968	0.20293	0.001
immediate recall	2	3*	1.25182	0.23001	0.001
Faces delayed	1	2*	1.51132	0.26924	0.001
Recognition		3*	1.10523	0.24947	0.001

Appendix C: Bonferroni Post-Hoc Comparisons: Significant Group Differences on Classification Variables for the Six-Cluster Solution

Classification Variable	(I) Wards6R	(J) Wards6R	Mean Difference (I-J)	Std. Error	Sig.
CVLT Trials 1-5	1	3	-1.10914	0.26890	0.002
		6	1.22956	0.23471	0.001
	2	5	1.23936	0.22840	0.001
		6	1.92040	0.21426	0.001
	3	5	1.65766	0.26341	0.001
		6	2.33870	0.25124	0.001
	4	5	1.01879	0.24769	0.002
		6	1.69984	0.23471	0.001
Taylor Complex Figure, 3rd recall	1	6	2.45098	0.74342	0.024
	2	6	3.51643	0.67864	0.001
	3	4	2.84250	0.85169	0.022
		6	4.51250	0.79578	0.001
	5	6	3.93273	0.72344	0.001
Digit Span Forward	1	2	1.33100	0.26189	0.001
		4	1.75300	0.28287	0.001
		5	1.85964	0.27637	0.001
		6	1.47886	0.26189	0.001
	2	3	-1.35250	0.28033	0.001
	3	4	1.77450	0.30003	0.001
		5	1.88114	0.29391	0.001
		6	1.50036	0.28033	0.001
Logical Memory Immediate Recall	1	6	1.43071	0.27848	0.001
	2	6	2.14286	0.25422	0.001
	3	6	2.17821	0.29810	0.001
	4	6	1.79671	0.27848	0.001
	5	6	1.35390	0.27100	0.001
Faces Delayed Recognition	1	2	-1.02614	0.30708	0.021
		3	-1.97525	0.35180	0.001
	2	4	1.62814	0.30708	0.001
		5	1.15442	0.29882	0.004
		6	1.19000	0.28032	0.001
	3	4	2.57725	0.35180	0.001
		5	2.10352	0.34462	0.001
		6	2.13911	0.32871	0.001

Appendix D: Bonferroni Post-Hoc Comparisons:

Significant IQ Differences for the 6-Cluster Solution

(I) Wards6R	(J) Wards6R	Mean Difference (I-J)	Std. Error	Sig.
1	6	23.75714	4.98944	0.001
2	5	16.27273	4.85534	0.021
	6	29.35714	4.55471	0.001
3	4	18.50000	5.71612	0.029
	5	21.27273	5.59945	0.005
	6	34.35714	5.34088	0.001
4	6	15.85714	4.98944	0.035

Appendix E: Volumetric Analysis of Groups Classified Based on Neuropsychological Test Performance (MRI Scans Divided Into Two Groups Based on Slice Thickness)

Brain volumes for the six primary regions of interest (ROIs) and the fourteen ROI combinations (right plus left volumes, right minus left volumes, etc.) were compared for patients who were clinically classified as having visuospatial deficits only, verbal plus visuospatial deficits, or no verbal or visuospatial deficits. Due to the small number of patients classified as having verbal deficits only, this group was not included in these analyses. Brain volumes for the three groups were analyzed using one-way ANOVA. One-way MANOVAs could not be used in any analyses due to small sample sizes. Bonferroni post-hoc pairwise comparisons were used applicable. All MRI scans were divided into two groups for volumetric analysis. The first group consisted of scans with slice thicknesses between 1.25 mm and 1.5 mm ("slicegroup 2;" n = 11). The second group consisted of: 1) scans with 1.0 mm slice thicknesses in which every other slice was measured, and 2) scans with 2.0 mm slice thicknesses ("slicegroup 1;" n = 15). The results of these analyses are found below.

"Slicegroup 1" (1mm and 2mm MRI Scans Only)

There were no significant difference in the brain volumes of patients with: visuospatial deficits only (n = 4), with both verbal and visuospatial deficits (n =6), or with no verbal or visuospatial deficits (n = 5).

"Slicegroup 2" (1.25 – 1.5mm MRI Scans Only)

There was a trend towards significantly smaller, $F(2, 7) = 5.59$, $p = .035$, right anterior temporal lobe volumes in patients who were classified by the author as having

both verbal and visuospatial deficits (M = 1.54, SD = .20, n = 4) compared to patients who were classified as having neither verbal nor visuospatial deficits (M = 2.34, SD = .53, n = 3). There was also a trend towards the sum of their right hippocampal, perirhinal, and anterior temporal lobe volumes (M = 2.03, SD = .21) being significantly smaller, $F(2, 7) = 5.40$, $p = .038$, than in patients who were classified as having neither verbal nor visuospatial deficits (M = 2.86, SD = .52). However, these differences were no longer significant after a Bonferroni correct p value of .0025 was applied. One-way MANOVA could not be used due to the small sample sizes.

Appendix F: Volumetric Analysis of Groups Classified by EEG/Neuroimaging (MRI Scans Divided into Two Groups Based on Slice Thickness)

Brain volumes for the six primary regions of interest (ROIs) and the fourteen ROI combinations (right plus left volumes, right minus left volumes, etc.) were compared using one-way ANOVAs for patients grouped by area of cortical damage or dysfunction based on EEG and/or neuroimaging. Bonferroni post-hoc pairwise comparisons were used where applicable. All MRI scans were divided into two groups for volumetric analysis. The first group consisted of scans with slice thicknesses between 1.25 mm and 1.5 mm ("slicegroup 2;" *n* = 11). The second group consisted of: 1) scans with 1.0 mm slice thicknesses in which every other slice was measured, and 2) scans with 2.0 mm slice thicknesses ("slicegroup 1;" *n* = 15). The results of these analyses are found below.

"Slicegroup 1" (1mm and 2mm MRI Scans Only)

Patients who were diagnosed with left temporal lobe damage or dysfunction based on EEG and/or neuroimaging (*n* = 8) did not differ significantly from patients not diagnosed with left temporal lobe damage or dysfunction (*n* = 7) on any of the temporal lobe MRI volumes.

"Slicegroup 2" (1.25 – 1.5mm MRI Scans Only)

Patients in slicegroup 2 who were diagnosed with left temporal lobe damage or dysfunction based on EEG and/or neuroimaging (*n* = 5) had lower mean left temporal MRI volumes than subjects not diagnosed with left temporal lobe damage or dysfunction (*n* = 6; see Table E1). However, after a Bonferroni corrected *p* value of .0025 was

applied, there was only a trend towards significance for the following MRI variables: 1) left hippocampal volume $F(1, 9) = 13.86$, $p = .005$; 2) bilateral hippocampal volume, $F(1, 9) = 9.78$, $p = .012$; 3) left hippocampal plus left perirhinal volume, $F(1, 9) = 11.87$, $p = .007$; and 4) combined bilateral hippocampal and perirhinal volumes, $F(1, 9) = 9.33$, $p = .014$. One-way MANOVA could not be used due to small sample size.

For both slicegroup 1 and slicegroup 2, subjects diagnosed with right temporal lobe damage or dysfunction based on EEG and/or neuroimaging ($n = 7$ and $n = 6$, respectively) had lower mean right temporal MRI volumes than subjects not diagnosed with right temporal lobe damage or dysfunction ($n = 8$ and $n = 5$). However, none of the volume differences were significant.