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Memory Performance in Children with Temporal Lobe Epilepsy: Neocortical vs. Dual Pathologies

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MEMORY PERFORMANCE IN CHILDREN WITH TEMPORAL LOBE EPILEPSY: NEOCORTICAL VS. DUAL PATHOLOGIES

by

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ABSTRACT

This study investigated memory in children with temporal lobe epilepsy and the ability to discern hippocampal dysfunction with conventional memory tests that are typically used to detect more global memory impairment. All data was obtained retrospectively from the epilepsy surgery program at a local children's hospital. The research population consisted of 54 children with intractable epilepsy of temporal onset, balanced across pathology types (with and without hippocampal disease) and other demographics. Each was given a clinical battery prior to surgical intervention, which included the WRAML/WRAML2 Verbal Learning subtest from which the dependent variables for this study were extracted.

The research hypothesis had predicted that memory retention between verbal learning and recall would be worse for participants with pathology that included hippocampal sclerosis than for those with non-hippocampal temporal lobe pathology. A two-way mixed-design ANOVA was used to test the hypothesis, which allowed incorporation of variables of interest related to memory factors, pathology type, and hemispheric laterality, as well as their various interactions. There was a significant main effect for change in the number of words retained from the final learning trial to the delayed recall. Although the interaction between memory retention and pathology type was not statistically significant, the average of the memory scores as it related to pathology by side did show significance. Thus, results did not support the hypothetical relationship between retention and hippocampal function. However, additional exploratory analyses revealed that the final learning trial by itself was associated with hippocampal pathology, which applied only to those participants with left-hemisphere

lesions. Logistic regression with the final learning trial correctly classified 74 percent of participants into the appropriate pathology category, with 81 percent sensitivity to hippocampal dysfunction.

Mean participant memory scores were nearly one standard deviation below the normative mean for both delayed recall and total learning scaled scores, regardless of pathology type or lesion hemisphericity. Thus, while the conventionally used indices of the WRAML Verbal Learning test are useful for determining overall memory status, they are not specific to pathological substrate. The within-subject main effect showed an expected loss of information across the time of the delay, but overall the recall score showed no association with hippocampal functioning.

This study revealed the possibility of measuring hippocampal function at statistically significant group levels using learning scores from a widely used measure of verbal memory, even in participants with intact contralateral mesial temporal structures. It also indicated that hippocampal structures do not play a role during recall measures given after a standard time delay. Data further demonstrated a role of the hippocampus for encoding and transferring information beyond short term/working memory into long term. During the learning process, the hippocampus appears to work in concert with short-term memory systems, but does not take over the encoding process until enough repetitions have occurred to saturate the working memory buffer. This research represents a small, yet important step forward in our understanding of the hippocampus, with potentially important implications for the future study of memory constructs and mensuration.

CHAPTER I: STATEMENT OF THE PROBLEM

Memory is a primary feature of human cognition and is necessary for completion of daily tasks from the very mundane to the most creative. Without functional memory, our ability to fulfill academic, vocational, or even recreational pursuits would be virtually impossible. However, despite considerable research efforts, memory may be the most complex yet least understood of all cognitive domains.

Declarative memory processes transform perceptual information into enduring pseudo-sensory representations via functional networks that synchronously engage multiple anatomical regions (Helmstaedter, Grunwald, Lehnertz, Gleibner, & Elger, 1997). In normal subjects, aspects of the neocortex and mesial temporal areas are functionally intertwined (Eichenbaum et al, 1996). However pathological damage to one component of the network can affect the entire network's function, leading to impaired declarative memory (Jones-Gotman et al., 1997). While memory impairments are very likely to occur in cases of temporal lesions, they may also be caused by frontal damage (Jambaque et al., 1993).

Studies of individuals with bilateral mesial temporal resection have validated the principle importance of the hippocampus for episodic memory encoding (Milner, Corkin, & Teuber, 1968; Scoville & Milner, 1957). However, isolating hippocampal memory functions from other basic cognitive processes has been difficult because they are so closely intertwined (Glosser et al., 2002). Localizing mesial temporal damage is further complicated by the inherently reconstructive nature of memory, as described by Loftus and Palmer (1974). After encoding, memory traces are believed to be stored in various parts of the cortex, dependent upon associated sensory modality. If these traces are

adequately stored, they may be put back together to form coherent memories, but the role of mesial temporal structures in the retrieval process remains a topic of considerable debate.

Neuropsychological assessment has become a routine part of the presurgical epilepsy evaluation (Stanford & Miller, 2007). In conjunction with other members of the surgical team, the neuropsychologist assists in localizing cerebral dysfunction and advises when cognitive losses may be expected following resection (Harvison, Griffith, & Grote, 2006). Unfortunately, neuropsychological measures often fall short in identifying isolated dysfunctional structures because normative scores reflect gross cognitive processes made up of many elemental subprocesses. They often lack the sensitivity to detect specific areas of memory deficiency, such as hippocampal functioning and material-specific lateralization (Wisniewski, Wendling, Manning, & Steinloff, 2012).

These limitations also extend to research application of these measures, with added complexity due to methodological issues (Loring et al., 1988). Many studies of temporal lobe epilepsy have not accounted for underlying pathology (Cormack, Varga-Khadem, Wood, Cross, and Baldeweg, 2012), highlighting a failure to differentiate between lateral and mesial lesions. Discriminative power may also be influenced by test selection and the nature of test stimuli (Mabbott & Smith, 2003).

Children with intractable seizures frequently have neuropsychological impairments (Nolan et al., 2004). In those with temporal lobe foci, memory deficits are especially common, even when IQ scores are within the normal range (Guimaraes, Li, et al., 2007). Furthermore, pediatric patients with refractory temporal lobe seizures often

have impaired executive skills (Rzezak et al., 2007). Rzezak, Guimaraes, Fuentes, Guerriero, and Valente (2012) found an association between executive dysfunction and episodic memory in children with temporal lobe epilepsy, but no indication of causality between them. The relationship between deficient encoding and retrieval mechanisms and executive impairment is suggested by greater impairment of recollection than recognition in patients with frontal lesions (Wheeler, Stuss, & Tulving, 1995). However, questionable hippocampal involvement in these processes and potential participation of parahippocampal structures further obscures the ability to evaluate isolated memory processes with readily available neuropsychological tests. Assessing these functions in children becomes even more complex due to numerous developmental issues that do not apply to adults.

In sum, memory complexity confounds the ability to use conventional neuropsychological data to adequately evaluate fundamental cognitive operations. Given these limitations, research is needed to explore more appropriate evaluation methods. This knowledge would enhance surgical decision making and provide patients and their families with more accurate estimates of postsurgical cognitive outcome. It would also potentially assist with rehabilitative strategies, suitable educational placement, and evaluation of therapeutic effectiveness in children with brain lesions.

CHAPTER II: REVIEW OF THE LITERATURE

Memory

Conceptual Overview

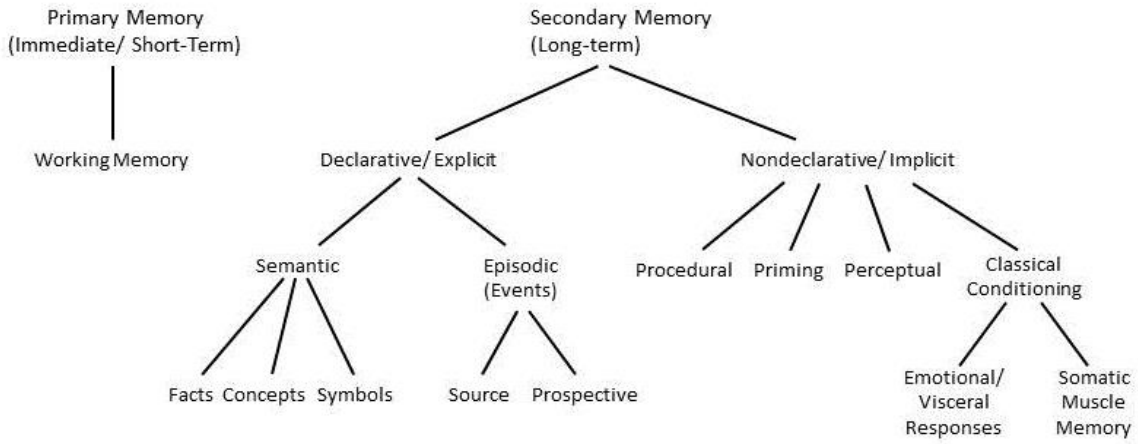
As a fundamental component of human cognition, memory encompasses the acquisition, storage, and retrieval of information (Meeter & Murre, 2004), including past events or experiences, factual knowledge, external perceptions and internally generated thoughts. This also provides the basis for anticipating future events as well as storing formulated plans, and enables the development of strategies. Because multiple cognitive processes are required to process such information, memory is clearly not a unitary construct (Paller, 2006), which greatly increases the complexity of its study.

Eichenbaum (1997) appropriately pointed out that memory can be viewed from numerous perspectives. Neuroanatomically, a memory system may be conceptualized as a series of neural circuits that work together to subserve a single memory function, or conversely as one larger network that mediates multiple types of memory. From a psychological frame of reference, these systems work collaboratively to support the performance of cognitive tasks, thus providing a functional explanation of how various sensory modalities are integrated in memory. Eichenbaum (1997) also presented the viewpoint that perhaps 'memory is not an entity at all, but rather a reflection of the plasticity [sic] properties that characterize each functional circuit of the brain."

Mammalian memory concepts, particularly those pertaining to humans, have gradually evolved into models that help explain various inter-related processes. One of the first was the Atkinson and Shiffrin (1968) "multi-store" model, which included long-term, short-term, and sensory processes. Since then, numerous authors have proposed

proprietary taxonomies; most have substantial commonality between primary components, with greater differences in the details. A common organizational scheme is depicted in figure 1. The various categories and divisions within this classification structure serve as heuristics for understanding mental processes and relating these to neuroanatomical substrates.

Figure 1: Common Taxonomy of Various Memory Types



In line with the hypothetical framework driving the present research, this review focuses on declarative memory; however because this cannot be isolated from other cognitive processes, an introduction to related elements is also provided.

Knowledge of primary or temporary memory storage is prerequisite to studying long-term memory. In his address to the Eastern Psychological Association in 1955, Miller (1956) proposed that the amount of information one could remember in one exposure ranges between five and nine items, depending on the type of data. Miller's "magical number seven, plus or minus two" thereafter became recognized as the capacity of primary memory. While short term and working memory are frequently treated as

synonymous, there are both similarities and differences. Both are time-limited and have a limited capacity, but working memory has the distinction of actively holding information in a short-term buffer so it can be processed or manipulated (Strauss, Sherman, & Spreen, 2006). Working memory is required for continually updated processes such as computations, and flexible, problem-solving behaviors (Cantor, Engle, & Hamilton, 1991).

Declarative memory is that ability which allows one to remember prior autobiographical episodes and complex facts (Squire, 1987). The terms declarative and explicit memory are often used interchangeably, and are assessed using tests of recall and/or recognition of facts and episodes. Tulving (1972) introduced episodic and semantic memory as two subtypes of declarative memory with very different properties. Episodic memory provides for conscious recollection of prior personal events or "episodes" in one's life. Recall of such experiences is linked with specific situations, places, and times related to acquisition of that information. Storage of episodic information is thus referenced to existing stores of autobiographical memory. In contrast, semantic memory is factual knowledge about the world, such as meaning of words, concepts, and objects, but independent of time or place. According to Tulving, information stored within each system has the potential of affecting the other; thus, registration of episodic information may be influenced by information held within semantic memory, while storage or retrieval of factual information can depend heavily upon its integration with autobiographical memories.

Several different types of implicit memory have also been identified, which do not require intentional encoding or even awareness that information is being registered.

Unlike explicit memory, implicit memory is below the threshold of conscious awareness (Papanicolaou, 2006), without involvement of executive processes or strategies (Baddeley, 1997). Priming refers to improvements in perceptual recognition of objects due to prior exposure, but independent of conscious recollection of the previous encounter (Schacter, 1992). Classical conditioning involves an unconscious association between two stimuli based upon sequential occurrence, one of which triggers an automatic response (Paller, 2006). Procedural memory is storage of motor skills, habits, mannerisms, and other temporally ordered sequences (Papanicolaou, 2006).

Mnemonic Functions of the Temporal Lobes

Mesial Temporal Lobe. A role of the mesial temporal region in memory function had been suspected since the early 1900's (DeJong, 1973) and was confirmed when Scoville and Milner (1957) published the neuropsychological outcomes of bilateral hippocampal resection in a series of nine patients (and one unilateral case). The most famous of these subjects was known as "H.M.", a bright, emotionally stable man who underwent this radical procedure to relieve incapacitating and medically refractory seizures. Prior to this time, mesial temporal lobe surgery had been used only as a treatment for severe psychoses, although without significant therapeutic effect. The resection performed on H.M. by Scoville removed the greater part of the hippocampi on both sides, extending 8 cm posteriorly from the temporal horns.

Following surgery, H.M. was unable to create any new personal memories but had "vivid and intact" remote memory; that is, he retained most memories acquired from years prior to the surgery. He did have some retrograde amnesia for select events such as the death of an uncle several years earlier. He maintained an above-average IQ, and since

his comprehension and reasoning remained intact, had no difficulty interacting normally in conversation. Despite these intact abilities, H.M. had no conscious recollection of tasks performed many times over again (Scoville & Milner, 1957). Many years later he continued to be globally amnestic, with impaired recall, regardless of the stimulus modality. He had good perceptual skills and short-term retention of information such as task instructions. Although he demonstrated a limited capacity for learning simple mazes, particularly tactile mazes, he never achieved error-free performance (Milner, Corkin, & Teuber, 1968). His motor task learning was also much slower than normal, but he did show consistent improvement across days of testing and retention of simple visuomotor skills for up to a year (Corkin, 2002). Despite his amnesia, H.M. was able to accurately describe the layout of the home he moved into following his surgery, where he lived for many years (Corkin, 2002). He also demonstrated normal long-term recognition of pictures. Even after 6 months, he was able to recognize magazine pictures he had studied for 20 seconds each, despite no memory of having seen them before (Freed, Corkin, & Cohen, 1987).

H.M. also demonstrated intact immediate memory. He was able to recall a three digit number for up to 15 minutes, maintaining such verbal material through continuous rehearsal (Milner, 2005). However, as soon as his attention was diverted and rehearsal disrupted, the information was lost. H.M.'s digit span pattern has been of considerable interest to researchers. Despite the capacity to flawlessly repeat six digits, he was unable to mimic a seven-digit string regardless of the number of trials presented (Jeneson, Mauldin, & Squire, 2010; Milner, Corkin, & Teuber, 1968).

While H.M. remains the most salient case study of mesial temporal memory functions, several patients with similar lesions have verified the original findings. Zola-Morgan, Squire, and Amaral (1986) reported on R.B., a middle aged man who experienced severe anterograde amnesia following an ischemic event related to complications of cardiac surgery. Postmortem evaluation five years later revealed almost complete cell loss of the CA1 area of the hippocampus bilaterally, with the remainder of the mesial temporal lobes essentially intact. Three comparable cases with isolated memory impairment were subsequently reported ten years after R.B. (patients G.D., L.M., and W.H.); MRI revealed bilateral hippocampal damage in all three cases, which was confirmed by neuropathology at death (Rempel-Clower, Zola, Squire, & Amaral, 1996). As with H.M., all four of these patients had normal IQ scores, impaired declarative memory with normal implicit memory performance, and greatest sparing of remote memories. Like R.B., G.D.'s damage was restricted to the hippocampi, with a small infarction of the right globus pallidus. L.M's hippocampal damage was slightly more extensive than the others. Both L.M. and W.H. demonstrated more extensive cell loss within the left hippocampus, and each demonstrated significantly more retrograde amnesia than H.M. and R.B. L.M.'s loss of prior memories extended back approximately 15 years. W.H. had greater sparing of CA1 neurons than the others but paradoxically showed worse retention of new materials than the others across all modalities as well as extensive, temporally-graded amnesia going back 25 years. Each remained cognitively stable from the time of their first evaluation until their deaths (average of 7 years).

Despite evidence of the essential role of the mesial temporal region for declarative memory formation, the intrinsic functions of the hippocampus remain somewhat

enigmatic. The relational nature of hippocampal neurons has been demonstrated by the response of single rat cells to associated stimuli during performance of memory and learning tasks (Eichenbaum, Cohen, Otto, & Wible, 1992). However, anterior and posterior portions of the hippocampus appear to be disconnected from one another (Colombo, Fernandez, Nakamura, & Gross, 1998), with multiple distinct circuits for processing different types of memory (Moser & Moser, 1998). Functional MRI has demonstrated that dentate gyrus and Cornu Ammonis (CA) fields are more active during encoding, while the subiculum was more active during retrieval (Eldridge, Engel, Zeineh, Brookheimer, & Knowlton, 2005).

Parahippocampal structures are also known to play roles in learning and memory, but their precise functions are only partially understood. It is believed that neurons in the hippocampus and parahippocampal areas perform different, but complementary memory functions (Suzuki & Eichenbaum, 2000). Significant knowledge has been gained through translational animal research because it allows ablation of homologous brain regions, where such experimentation in humans is not possible. Limitations remain due to neuroanatomical differences across species, particularly with regard to structures that subserve verbal cognitive functions. Nonetheless, these studies have revealed a perceptual role of mesial temporal areas, in addition to mnemonic functions (Lee et al., 2005). Animal studies have also demonstrated functional independence of the mesial temporal structures; whereas hippocampal lesions lead to impaired spatial cognition, lesions of the perirhinal and postrhinal cortex impair object recognition (Winters, Forwood, Cowell, Saksida, & Bussey, 2004). Disrupted object recognition by transient inactivation of the perirhinal cortex further evidences the importance of this area in

encoding and retrieval (Winters & Bussey, 2005). The essential nature of the perirhinal cortex for visual paired associate and configural learning has also been established through primate experimentation (Buckley & Gaffan, 1998).

A potential role of novelty detection by parahippocampal areas was highlighted by H.M.'s recognition of previously seen pictures despite hippocampal absence (Corkin, 2002). This role is supported by fMRI activation of the perirhinal cortex during encoding of novel picture pairs in human subjects (Pihlajamaki et al., 2003). The perirhinal cortex also participates in verbal memory encoding, as demonstrated by fMRI activation that was greater when encoding words that were subsequently remembered than those not successfully registered (Strange, Otten, Josephs, Rugg, & Dolan, 2002).

Temporal Neocortex. While the mesial temporal structures are clearly vital components of the declarative memory system, research on the precise mnemonic functions of the temporal neocortex has not been as conclusive. Neither Giovagnoli and Avanzini (1999) nor Jones-Gotman et al. (1997) reported significant performance differences related to temporal lesion location in adults. However, Mueller et al. (2013) provided evidence of differing structures associated with memory impairments in temporal lobe epilepsy. In patients with hippocampal foci, the deficits were related to hippocampal and prefrontal volume loss; those with neocortical foci showed a much lesser degree of mesial temporal volume loss. Perhaps the most striking differences relevant to temporal lesion location were noted by Helmstaedter et al. (1997), who indicated specific impairment patterns: Mesial lesions were related to poor consolidation, while neocortical lesions were associated with working memory and encoding deficits. Pediatric comparisons have also varied in their conclusions. Although Gonzalez,

Anderson, Wood, Mitchell, and Harvey (2007) revealed a greater probability of mnemonic deficits in children with mesial than lateral temporal seizure foci, Nolan et al. (2004) found no differences.

Numerous investigations have suggested an important role of the anterior temporal lobe (ATL) in semantic memory. While the precise boundaries of the ATL are somewhat ill-defined, it generally refers to the temporal pole, anterior aspects of superior and middle temporal gyri, and parts of the fusiform and parahippocampal gyri (Bonner & Price, 2013). Atrophy of the ATL is frequently accompanied by pronounced difficulties in retrieval of semantic information (Rogers et al., 2006). While semantic memory shows greater disruption in patients with left anterior temporal lesions, right-sided temporal neocortex may also play an important role in semantic memory representations (Ralph, Ciplotti, Manes, & Patterson, 2010).

Amnestic patients with bilateral hippocampal damage often demonstrate relatively preserved semantic memory, despite severely impaired episodic retention (Schmolck, Kensinger, Corkin, & Squire, 2002). Kitchener, Hodges, and McCarthy (1998) reported on the case of a 49-year-old man with amnesia due to total destruction of the left hippocampus, parahippocampal gyrus, entorhinal and perirhinal cortices following a cerebro-vascular event 13 years earlier. His amygdala and temporal pole were both spared. The man was unable to recall any personally experienced episodes from any period of his life, but had no insight regarding his deficits. Despite inability to remember major autobiographical events, he retained some ability to acquire new semantic knowledge, particularly vocabulary and facts. Similar cases in children have been reported by Vargha-Khadem and colleagues (1997). They detailed observations of three

children with bilateral hippocampal pathology who were amnestic to personal experiences, but still able to attend school, learn factual knowledge, and attain general academic competence within the low average to average range. By contrast, all three had very poor temporal and spatial orientation, highly impaired autobiographical memories as and little recall of the day's events, including interactions, trips, and special occasions.

Such an anatomical dissociation for declarative memory subtypes is very oversimplified (Hoscheidt, Nadel, Payne, & Ryan, 2010) and remains controversial. Despite evidence for localization of semantic memory functions, other data supports the view that mesial temporal structures play an important role in semantic memory (Squire & Zola, 1998). Limited semantic deficits in H.M. and other patients with bilateral hippocampal damage have suggested that mesial temporal structures are important for acquisition and storage of semantic knowledge (Manns, Hopkins, & Squire, 2003; Schmolck, Kensinger, Corkin, & Squire, 2002). Semantic impairment has been noted in adults with left hemisphere epilepsy regardless of whether seizures were temporal or extratemporal (Giovagnoli, 2005). Messas, Mansur, and Castro (2008) also found impaired semantic memory in adult epilepsy patients with lesions restricted to the hippocampus. While semantic performance was diminished for both left and right TLE compared with controls, those with left-sided foci had significantly greater impairment in defining words. Atrophy observed in semantic dementia patients frequently includes areas of the perirhinal cortex, while sparing the adjacent posterior temporal neocortex (Davies, Halliday, Xuereb, Kril, & Hodges, 2009). Furthermore, functional MRI has shown activation of the temporal neocortex as well as the hippocampus on both episodic and semantic memory tasks in healthy adults (Hoscheidt, Nadel, Payne, & Ryan, 2010;

Menon, Boyett-Anderson, Schatzberg, & Reiss, 2002) suggesting both are important substrates of general declarative memory.

Neuroanatomy of the Mesial Temporal Region

From a gross perspective, the mesial temporal lobe is comprised of the hippocampal formation and the parahippocampal gyrus. The hippocampus proper (named for its resemblance of a seahorse) is oriented with its arched structure terminating near the splenium of the corpus callosum, and has been regarded by some as an extension or "appendage" of the neocortex (Amaral & Lavanex, 2007) despite differences in cytoarchitecture. During fetal development, the hippocampus progressively infolds upon itself twice, forming the characteristic S-shape within the remainder of the temporal lobe (Kier, Kim, Fulbright & Bronen, 1997). Fully developed, the head of the hippocampus is immediately caudal and inferior to the gray matter of the amygdala (Tein, Feisberg, & Crain, 1992). The hippocampus proper consists of the cornu ammonis (literally "Ammon's horn") and dentate gyrus, which are separated by the hippocampal sulcus, an embryonic fissure between the two. The CA is divided into four parts, known as CA1 through CA4, which are linearly aligned. CA1 is the largest and outermost aspect, extending from the subiculum to CA2. This in turn transitions to CA3 at the infolding by the dentate gyrus, while CA4 is surrounded on its exterior boundary by the dentate. The left and right hippocampi communicate directly through the interhippocampal commissure, a white matter bundle that may also provide a pathway for the spread of seizures from an epileptogenic hippocampus to the contralateral side one side to the other (Khalilov, Holmes, & Ben-Ari, 2003).

The structural network in which the hippocampus resides is often referred to as the Papez circuit or medial limbic network. This system connects the hippocampus with the temporal and frontal lobes using the following components linked in series: Entorhinal cortex, hippocampus, fornix, anteromedial thalamus, mammillary body, cingulum, and parahippocampal gyrus (Shah, Jhawar, & Goel, 2012). The parahippocampal gyrus sits inferior and lateral to the hippocampal formation, comprised primarily of the entorhinal, perirhinal, and parahippocampal cortices, and provides the majority of links between cortical and mesial temporal structures.

The entorhinal cortex is the most visually prominent part of the mesial temporal region, located in the anterior portion of the parahippocampal gyrus adjacent to the subiculum (Amaral, 1999) and serving as the major bidirectional conduit between the hippocampus and neocortical association areas (Fitzgerald, Gruener, & Mtui, 2007). Two-thirds of information from polymodal association areas in superior temporal, prefrontal, and parieto-occipital cortices reaches the entorhinal cortex via the perirhinal and parahippocampal cortices, with the remainder reaching the entorhinal cortex directly (Burwell, 2000; Insausti, Amaral, & Cowan, 1987). The subiculum is essentially the continuation of the cornu Ammonis and thus connects the entorhinal cortex with the HPc. The perirhinal cortex is lateral to the rhinal sulcus. The lateral border of the PRc extends into the inferotemporal gyrus and extends anteriorly into the medial part of the temporal pole (Suzuki, 1996). The parahippocampal cortex occupies the posterior part of the parahippocampal gyrus. Perirhinal and parahippocampal cortices serve as the primary pathways for information between sensory association cortex and the hippocampus, via the entorhinal cortex.

There are additional connections between the hippocampus and frontal lobes. The ventral portions of CA1 and the subiculum have dense monosynaptic projections to the ventral medial prefrontal cortex (LaRoche, Davis, & Jay, 2000). As revealed by anterograde tracers injected into the rat brain, CA1 also has fibers running to the medial orbital cortex (Hoover & Vertes, 2007; Jay & Witter, 1991). Perirhinal and entorhinal cortices also project directly to the ventral medial prefrontal cortex (Hoover & Vertes, 2007).

Several areas of the diencephalon also play important roles in memory, primarily for recall of episodic information. Subcortical inputs to the hippocampus via the fornix include the amygdala, thalamus, and septal nuclei. The amygdala plays a role in emotionally-linked memory, but damage otherwise has little effect upon declarative memory performance (Kolb & Wishaw, 2009). While the diencephalic system is very important for declarative memory (Van derWerf et al., 2003) it is beyond the scope of this paper and will not be discussed further. A comprehensive review of the diencephalic memory system may be found in Zola-Morgan and Squire (1993).

Hemispheric Memory Specialization

Hemispheric lateralization for material-specific episodic memory has long been a neuropsychological concept, with some adult studies finding a hemispheric double-dissociation whereby right hemisphere lesions caused visual memory impairment and left side lesions affecting verbal memory (Lezak, Howieson, & Loring, 2004). In a series of 70 epilepsy surgery patients, Chiarvalloti & Glosser (2001) demonstrated verbal memory decline following left temporal lobectomy, while those with right temporal resection declined in visospatial memory. In a more recent study, Bonelli and colleagues (2010)

demonstrated a similar relationship using fMRI activation; they found a positive correlation between left hippocampal activation and verbal memory performance, while right hippocampal activation was related to proficiency in design learning. By contrast, however, numerous adult studies have noted left lateralization of verbal memory, but non-lateralized visual memory. In a comprehensive review of this topic, Saling (2009) concluded, "verbal and non-verbal memory are not opposites in terms of their respective patterns of cerebral organization." A number of studies have found verbal memory deficits in patients with left TLE but non-lateralized visual memory (Alessio et al., 2006; Baxendale et al., 1998; Bonilha et al., 2007; Sawrie, et al., 2001). At least one adult study was unable to determine reliable lateralization of either verbal or non-verbal memory in patients with TLE (Hermann, Seidenberg, Haltiner, & Wyler, 1992). Non-verbal memory measures have been much less lateralizing and generally shown to be poor indicators of right mesial temporal dysfunction in adults (Kneebone, Lee, Wade, & Loring, 2007; Moore & Baker, 1996; Wilde et al., 2003). In addressing the variability of findings, Jeyaraj et al. (2013) cautioned that particular characteristics of the tasks used are likely to influence their ability to lateralize impairments.

Despite findings of verbal memory lateralization in the adult literature, there is considerably less systematic evidence of this phenomenon in pediatric populations (Laurent & Arzimanoglou, 2006). Most studies of verbal memory in children with TLE have found no relationship between seizure laterality and verbal memory deficits (Jocic-Jakubi & Jovic, 2006; Kar, Rao, Chandramouli, Thennarasu, & Satishchandra, 2010; Lendt, Helmstaedter, & Elger, 1999; Nolan et al., 2004). Exceptions to this include Jambaque, Dellatolas, Dulac, Ponsot, and Signoret (1993), who discovered dissociable

memory patterns in children similar to those in adults, and Gonzalez et al. (2007), who noted a significant relationship between right temporal dysfunction and non-verbal memory. While Mabbott and Smith (2003) found no relationship between verbal memory and seizure lateralization, they did find impaired face recognition memory in children with right temporal lesions.

Lateralization of verbal memory has demonstrated a strong relationship with propositional language hemisphericity, particularly in epilepsy patients. Labudda and colleagues (2010) described an association between left language fMRI activation and verbal memory decline following left mesial temporal resection in adult TLE patients. In children with seizures, Everts et al. (2010) found a significant association between side of fMRI language activation and hippocampal memory activation. In another study of adults with temporal lobe epilepsy, those with left-sided language dominance and left seizure focus had better non-verbal memory capacity (Kim, Yi, Son, & Kim, 2003). In each of these studies, patients with left-sided seizure focus and atypical language dominance had better verbal memory scores than those with traditional language laterality. Hermann et al. (1992) noted verbal memory differences between left and right temporal foci on the California Verbal Learning Test; however these became insignificant once they controlled for language function.

Verbal memory lateralization appears to be related primarily to temporal neocortical structures, as mesial temporal areas have shown no modal bias. Helmstaedter et al. (1997) evaluated 60 adults with left temporal lobe epilepsy and left language dominance to differentiate this aspect of mesial and lateral temporal lobe function. Memory and Wada testing were performed on all patients; and 32 underwent intracranial

event–related potential recordings during a word recognition paradigm. The authors concluded that mesial temporal areas were modality-neutral for their role in long-term consolidation and retrieval, while the lateral temporal lobe supported language-specific memory functions. These inferences were further reinforced by Binder et al. (2010) who published language lateralization and verbal memory results following left temporal lobectomy. They studied 30 adults with left temporal lobe epilepsy prior to and following resective surgery. Postoperative verbal memory decline was associated with language laterality, but not with asymmetrical fMRI activation of the hippocampi during scene encoding.

Differences in verbal memory lateralization between adults and children may be further explained by two factors: (1) the developmental transition of language from pure visual to a combination of visual and verbal processes during the grade school years (Cramer, 1976) and increased hemispheric language specialization. Multiple fMRI studies of the degree of language lateralization have shown a progressive increase with age from early childhood through adolescence and early adulthood (Everts et al., 2009; Holland et al., 2001; Szaflarski, Holland, Schmithorst, & Byars, 2006). The literature also supports age-related hemispheric lateralization of general cognitive processes (Moses et al., 2002) and short-term visuospatial memory (Groen, Whitehouse, Badcock, & Bishop, 2012). Such a developmental pattern for declarative memory was documented by Gonzalez, Mahdavi, Anderson, and Harvey (2012) in their evaluation of children with temporal lobe epilepsy longitudinally from childhood to young adulthood. In those with left seizure foci, verbal memory was worse at maturation (mean age 16.10 years) than it

had been during childhood, which might reflect either progressive memory lateralization or merely advancing memory decline.

Development of Declarative Memory

As indicated earlier, most current notions about the neurological substrates of memory are derived from adult studies. Conversely, there is relatively little known about biological mechanisms involved in childhood memory development. While numerous books and reviews have documented memory status across the lifespan, a minority have integrated memory changes with neural substrates maturation. As indicated by Bauer (2007), there has been considerable recent focus on memory development in infants and toddlers, almost to the neglect of preschool and later years. In preverbal children, paradigms and techniques similar to those used to study memory in nonhuman primates are often used (Nelson, 1995), despite significant differences between the species.

Improved memory over the course of childhood results from maturation of neuroanatomical structures and connectivity between them (Demaster & Ghetti, 2013; Ghetti & Bunge, 2012). Structurally, the mesial temporal structures develop relatively early in life, with all areas of the hippocampal formation identifiable at birth (Insausti, Cebada-Sanchez, and Marcos, 2010). The prefrontal cortex, by contrast, develops relatively late (Ofen et al., 2007), with prolonged myelination of axons, particularly those of the lateral prefrontal cortex, where aspects of executive control are coordinated (Fuster, 2002). Despite functional and anatomical immaturity of the dorsolateral prefrontal cortex working memory is almost fully mature by age 9 to 10 (Farber & Beteleva, 2011). Hippocampal-dependent registration develops in the first few months of life (Nelson, 1995), with mesial temporal activation observed during encoding in early

childhood and decreasing with age (Maril et al., 2010). Early childhood encoding relies predominantly on perceptual networks; with increasing age frontal structures gradually assume a more important role (Maril et al., 2011). fMRI studies also demonstrate hippocampal activation from an early age during recall, although considerably more robust in adolescents and adults (Ghetti, DeMaster, Yonelinas, & Bunge, 2010).

It is well-recognized that memory performance generally improves as children mature, with greater memory plasticity in the nascent brain (Shing & Lindenberger, 2011). Episodic memory involves an interaction between "associative" and "strategic" components. Whereas the capacity to form and store associations is relatively mature by mid-childhood, the use of memory strategies does not develop until somewhat later (Shing & Lindenberger, 2011), coinciding with the maturation of executive functions. According to Anderson, Northam, Hendy, and Wrenall (2001) executive abilities undergo growth periods from birth to age two, from seven to nine years old, and between 16 and 19 years of age. Rhodes, Murphy, and Hancock (2011) found verbal strategies aiding memory retrieval beginning at age 10. Early memory performance is also limited by inexperience. A greater repertoire of background knowledge is linked with greater capacity to bind related information (Srull, 1983). Thus, age-related improvements in fund of general knowledge (i.e., crystallized intelligence) may directly influence memory performance (Ofen, 2012). More sophisticated knowledge structures also facilitate better use of organizational strategies (Srull, 1983).

There is evidence that emerging language skills are an important factor in childhood memory maturation. While verbal expression of past events provides the earliest evidence of intentionally accessed memory in childhood, the onset of language

use marks an important event in memory development. Even in pre-verbal infants, verbal cues given by adults have been shown to facilitate memory performance (Hayne & Herbert, 2004). According to social-interactionist theory, linguistic development is a vital element of mental schemata (Sutton, 2002). Vygotsky (1978) described language as a tool that forms the basis of thought processes such as reasoning and problem solving. He further reasoned that internal and external speech also provide a conduit for learning, use of strategic thought, and behavioral regulation. Furthermore, language development appears to influence the emergence of certain memory strategies. Compared with normal children, children with prelingual hearing loss have noted delays in the evolution of systematic strategies (Bebko, 1998).

Memory Processes: Encoding, Storage, and Retrieval

There are several processes involved in successful execution of declarative memory: information that is perceptually captured is initially encoded and then stored, after which it may either be retrieved or forgotten. Encoding refers to the initial awareness, comprehension, and registration of stimuli (Paller, 2006). Experiences or stimuli perceived but not retained are processed very differently than those that are. Memory encoding is dependent upon the prefrontal cortex for organization of materials within the context of working memory (Blumenfeld & Ranganath, 2007; Fletcher, Shallice, & Dolan, 1998), while mesial temporal structures appear to support subsequent transfer into long-term storage. Schott and colleagues (2013) noted fMRI differences in neuroanatomical activity dependent upon the quality of stimulus encoding. Deeper encoding promoted by greater elaboration of stimuli leads to better retrieval than perceptual encoding alone (Craik & Tulving, 1975; Schott et al., 2013).

Declarative memories are believed to reside in various areas of the neocortex; however despite technological advances in mapping cognitive networks and their corresponding substrates, the exact details of memory formation and retrieval remain unknown. While mesial temporal areas appear to be crucial for formation and initial retrieval of memories, they become less important as information is gradually transferred and consolidated within the neocortex (Alvarez & Squire, 1994; Squire & Alvarez, 1995). Presumably, neurophysiological representations of experiences or stimuli must first be converted to a format or "trace" compatible with cortical storage (Pribram, 1971). Hebb (1949) postulated that simultaneous activation of neighboring neurons is responsible for memory storage and learning through increased synaptic strength between the involved cells. Hebb also introduced the concept of organized storage by related cortical function, whereby synaptic changes occur close to corresponding neocortical sensory regions.

Penfield and Perot (1963) presented one of the first accounts of cortical storage after they electrically stimulated the temporal neocortex of more than 1000 individuals during awake craniotomy for epilepsy surgery. In a small proportion of these patients, they elicited vivid recollection of past personal experiences or flashbacks. This procedure has been replicated numerous times (reviewed by Selimbeyoglu and Parvizi, 2010), with elicitation of various sensory and behavioral phenomena across the studies, depending upon the area stimulated. Jacobs, Lega, & Anderson (2012) suggested that such memories are evoked by altering neural circuits to approximate their normal status during memory retrieval. Cortical storage is also supported by animal studies in which damage

or inactivation to areas of the neocortex has produced selective memory deficits (Shema, Sacktor, and Dudai, 2007; Wiltgen, Brown, Talton, & Silva, 2004).

The process by which memory traces stabilize and become resistant to interference and decay is known as consolidation. Ribot (1882) described a time gradient commonly associated with amnesia, in which memories acquired earliest in life are the least vulnerable to loss due to brain damage. Furthermore, newest memories are the least stable, but are gradually strengthened over time (Wiltgen et al., 2004). Smith & Squire (2009) presented evidence for a reciprocal temporal relationship between mesial temporal lobe and cortical structures, whereby with the passage of time stored information relies more on the cortex and less on the hippocampus. Consolidation is enhanced by distributed learning, or spreading learning trials out over time, rather than having them all in a single session (Litman & Davachi, 2008). This essentially allows for initial consolidation of information before re-activation, which makes memories very resistant to decay.

Synapses between the prefrontal cortex and hippocampus are bidirectionally modifiable, contributing to long-term potentiation necessary for memory maintenance (Laroche et al., 2000). Signals between these structures are regulated through neuronal oscillations (Colgin, 2011). The nature of these oscillations varies with the type of information being relayed and its relevance to other cognitive processes (Benchenane, Tiesinga, & Battaglia, 2011). Oscillations within the theta band, and particularly their coherence between prefrontal and hippocampal regions, appear to be key in consolidation of memories (Benchenane et al., 2010). This process appears to be prominent during

slow-wave sleep, when there is strong synchronous communication between mesial temporal and frontal structures (Wierzynski, Lubenov, Gu, & Siapas, 2009).

As seen with patient H.M., remote memories eventually become independent of the hippocampus (Colgin, 2011). This has been attributed to remote memory storage in cortical areas of the brain, allowing other areas to autonomously retrieve memories. It could also have possible attribution to the changing nature of memory content over time. A time-dependent gradient has been reported for transformation of memory traces as they shed many of their details, becoming gradually more parsimonious (Furman, Mendelsohn, & Dudai, 2012; Nadel, Winocur, Ryan, and Moscovitch, 2007) Despite the observed correlation between hippocampal involvement in retrieval and loss of memory detail, the causative direction of this relationship remains unknown. The literature does not indicate whether remote memories become less dependent upon the hippocampus as a result of such changes to memory traces, or if they lose detail due to hippocampal disengagement. A related phenomenon was proposed by Cermak (1984), who described episodic memory being stripped of "when", "what," and "where" to become semantic in nature; under this model, newly acquired memories would have an episodic quality, with remote memories becoming more semantic over time.

Memory retrieval involves re-activation of memory traces, and depending upon the complexity of the memory, may require linking or reconstruction of episodic components (Kokinov, Petkov, & Petrova, 2007). Like the other processes, memory retrieval relies on interaction between the prefrontal and mesial temporal regions, often with reorganization of neural circuits (Osada, Adachi, Kimura, & Miyashita, 2008). Various executive skills are involved in both episodic and semantic memory retrieval

(Shimamura, 2002), with a greater executive burden for detailed recollection than familiarity tasks (Dobbins, Foley, Schacter, & Wagner, 2002). During retrieval, prefrontal regions typically show a greater response to familiar than unfamiliar stimuli (Xiang & Brown, 2004). The majority of retrieval processes are mediated by the left prefrontal cortex, but the precise anatomical substrate varies with the specific process (Shimamura, 2002; Xiang & Brown, 2004). Individuals with strong working memory skills successfully use organizational strategies during the learning phase and contextual cues during retrieval to a much greater extent with those with poor working memory (Spillers & Unsworth, 2011; Unsworth & Spillers, 2010).

Memory recollection may be either free or associative retrieval, while familiarity tasks are based on recognition of stimuli. There is some ongoing debate regarding the neuroanatomical substrates supporting differing types of retrieval. One view maintains that both recollection and familiarity are supported by hippocampal neurons (Rutishauser, Schuman, & Mamelek, 2008). The other indicates hippocampal mediation only for recollection (Yu, Johnson, & Rugg, 2012), which is consistent with familiarity supported by perirhinal cortex (Pihlajamaki et al., 2003). Several recent studies have provided a degree of clarity to this controversy by defining conditions under which the hippocampus is likely to be involved. Smith, Wixted, and Squire (2011) reported hippocampal involvement in both recollection and familiarity only when memories are robust. An argument has also been made for recollection as a continuous, rather than discrete process, and therefore both are supported by the same brain regions (Wixted, Mickes, & Squire, 2010). Furthermore, mesial temporal activity has demonstrated greater activation

with successful retrieval rather than just attempted retrieval (Nyberg, McIntosh, Houle, Nilssen, & Tulving, 1996).

Executive Functioning and Working Memory

Overview

Executive functioning (EF) constitutes a collection of cognitive skills required for many complex, goal-oriented behaviors (Elliott, 2003). While EF is difficult to define discretely, most sources conceptualize it as encompassing higher order cognitive processes, often involving control over other types of thought and behavior (Black, Semple, Pokhrel, & Grenard, 2011). Internal processes regulated by EF include information and knowledge processing, behavioral control, and metacognitive activities enabling introspection and self-monitoring (Chan, Shum, Toulopoulou, & Chen, 2008). Executive skills also include novel problem-solving that might require the flexibility to modify a strategy or behavior in the presence of new information (Elliott, 2003) as well as speculation of potential future outcomes so goal-directed strategies may be formulated (Jurado & Rosselli, 2007).

The accurate clinical assessment of executive skills may be confounded by conceptual issues. Common tests include general problem-solving ability, thought flexibility, fluency, planning, behavioral initiation, response inhibition, and deductive reasoning (Chan, Shum, Toulopoulou, & Chen, 2008; Strauss, Sherman, & Spreen, 2006), but these lack specificity because they require multiple skills, such as perception and motor output. Although once believed to measure purely frontal lobe dysfunction, it is often difficult to dissociate processes occurring in other anatomical zones. Data from clinical and imaging studies have linked these measures primarily to the frontal lobes,

especially prefrontal areas (Stuss & Alexander, 2000), but some additional variance has been attributed to other regions (McDonald et al., 2006). Thus, while the terms "executive function" and "frontal lobe function" continue to be used synonymously, this appears to be an overly simplistic conceptual view, as these functions depend upon integration with other cerebral areas across dynamic functional networks (Elliott, 2003; Stuss & Alexander, 2000).

Some authors include working memory under the umbrella of executive functions (Elliott, 2003). Others have conceptualized it as a type of "executive attention" (Engle, 2002), while factor analytic studies have established executive attention as a common element of both executive functioning and working memory (McCabe et al., 2010). Depending upon the executive process required by a specific working memory task, PET activation has been noted within either the dorsolateral or ventrolateral prefrontal cortex, or both (Owen, Evans, & Petrides, 1996; Owen, Lee, & Williams, 2000). However, more recent evidence of widespread working memory networks encompassing both neocortical and mesial temporal regions calls for reconsideration of some traditional working memory concepts (Poch & Campo, 2012; Stretton et al., 2012).

Role of Frontal Cortex in Explicit Memory

Executive processes mediated by the frontal lobes play an important role in various aspects of memory and learning. Functional imaging has demonstrated activation of left prefrontal cortex when subjects were tested on various episodic memory tasks (Dobbins et al., 2002). Cortical thickness within frontal areas has also been associated with verbal memory scores (Chang et al. 2010). While there is evidence connecting frontal lobe damage with disrupted declarative memory, there tend to be qualitative

differences in performance between frontal and temporal lesions (Ranganath & Knight, 2002). In comparing patients following epilepsy surgery, those with temporal resections had worse recall overall, but those with frontal resections struggled more with encoding and retrieval (McDonald, Bauer, Grande, Gilmore, & Roper, 2001). Wheeler, Stuss, and Tulving (1995) performed a meta-analysis on 21 studies exploring the relationship between the frontal lobes and memory. They determined that frontal lesions significantly disrupted memory function for free recall, cued recall, and recognition compared with normal controls. However, they also noted that frontal lesions differentially affected recall tests to a greater extent than recognition tests.

Declarative memory performance is highly dependent upon executive skills mediated by the frontal lobes, including working memory, vigilance, inhibitory control, and retrieval fluency (Baddeley, 1997; Head, Rodrigue, Kennedy, and Raz, 2008). Children are able to acquire simple factual information from an early age (Picard, Cousin, Guillery-Girard, Eustache, & Piolino, 2012) but greater executive ability is required for more novel or complex memory tasks (Busch et al., 2005). The prefrontal cortex is a primary substrate for processes associated with organization of learned information (Fletcher et al., 1998) and guides the encoding and retrieval of stored memory representations (Badre & Wagner, 2007; Blumenfeld & Ranganath, 2007). It supports long-term synaptic plasticity as part of the neural network controlling declarative memory (Jung, Baeg, Kim, Kim, & Kim, 2008). Along with progressive development of the frontal lobes, memory strategies such as rehearsal, elaboration, and organization generally improve as children mature (Ofen, 2012). Contextual recall of episodic memory is also highly reliant upon executive processes (Picard et al., 2012).

Relationship of Executive Functioning to Declarative Memory

Deficient explicit memory secondary to weak executive skills have been noted across populations with various neurological disorders. Hermann, Seidenberg, Lee, Chan, and Rutecki (2007) indicated 29 percent of adults with TLE had both memory and executive skills impairments, while 24 percent exhibited isolated memory impairment. Noel et al. (2012) evaluated memory recall and executive functioning in detoxified alcoholics. Compared with non-alcoholic controls, the alcoholic subjects had significantly worse performance on the California Verbal Learning Test. Stepwise regression revealed Trails B scores were strong predictors of immediate and delayed word list recall. In these subjects, EF deficits appeared to affect encoding and retrieval with intact information storage. Simard, Rouleau, Brosseau, Laframboise, and Bojansky (2003) found memory deficits that varied directly with executive abilities in adults with ruptured aneurysms of the anterior communicating artery. Those with poor executive functioning had the worst free recall, while recognition was still intact. Despite disparate etiologies, these patients demonstrated intact memory storage overall, with deficient retrieval of stored information.

In healthy older adults EF has been demonstrated as a significant mediator of episodic memory (Lee et al., 2012); however in the majority of aging studies, causal relationships have been less consistently found. Declines in both EF and memory in normal aging as well as Alzheimer's disease have been clearly documented (Bisiacchi et al., 2008). Degenerative brain changes in older adults generally manifest as deficient storage as well as poor application of strategies (Shing et al., 2010). Among individuals with Mild Cognitive Impairment (MCI) those with good EF have demonstrated better

episodic memory performance than those with more deficient executive skills (Chang et al., 2010). In older adults with MCI or dementia, greater volumes of MRI white matter hyperintensity have adversely affected both EF and episodic memory, although the relationship between EF and memory has varied among studies. Smith et al. (2011) found independent associations between these two factors and hyperintensity volume. Their study showed lesion location was the most important factor in predicting cognitive deficits. By contrast, Parks et al. (2011) reported mediation of hyperintensity effects upon episodic memory. Diminished executive skills have been noted in elderly with severe mesial temporal atrophy (Oosterman et al., 2012). Furthermore, hippocampal atrophy in Alzheimer's patients interacted with EF such that patients with decreased hippocampal volume and good EF had better episodic memory function than those with worse EF (Parks et al., 2011).

Working Memory

In discussing declarative memory, it is imperative to address working memory due to the associations between working memory, long-term memory, and their related neurological substrates. The ability to maintain and manipulate information has been highly correlated with intellectual and reasoning skills (Conway, Kane, & Engel, 2003; Poch & Campo, 2012). Numerous theoretical models of working memory have been proposed. Atkinson and Shiffrin's (1968) unitary memory model distinguished between "structural" systems for memory storage, and control processes to manipulate and transfer stored information. Along these lines, Baddeley and Hitch (1974) postulated that working memory utilized separate storage and control processes. However, their model is predicated upon multiple passive systems for temporary data storage with an independent

executive controlling system to manipulate the stored information. These slave systems include a verbally-based “phonological loop” and nonverbal “visuospatial sketchpad” with later addition of an episodic buffer (Baddeley, 2003). The phonological loop is the best-developed component of the model, conceptualized as a temporary warehouse for discrete verbal information (Baddeley, 2000). The episodic buffer has the theoretical capacity to bind information from the other working memory components as well as from long-term memory, thus modeling a unified gateway mechanism for multimodal episodic memory.

Medial temporal involvement in working memory continues to be controversial (Poch & Campo, 2012), as the interaction between hippocampal structures and prefrontal cortex is apparently more complex than previously recognized (Laroche et al., 2000). Hippocampal activation during working memory has not been seen universally however, but instead is systematically dependent upon the specific task demands (Laroche et al., 2000). Functional MRI studies by Takashima et al., (2006) identified common areas involved in declarative memory and certain working memory processes; sustained activation of the left frontal and right occipital regions were consistent with deeper encoding processes. fMRI has also demonstrated bilateral hippocampal activation during maintenance of unfamiliar faces (Ranganath & Esposito, 2001).

Olson, Moore, Stark, and Chatterjee (2006) found impaired visual working memory in patients with mesial temporal lesions when stimuli could not be verbally recoded. Working memory was also disrupted in adults with epilepsy due to mesial temporal sclerosis, regardless of laterality of pathology (Stretton et al., 2012). However, intact working memory has been reported in adults (Tudesco et al., 2010) and children

(Cormack et al., 2012) with temporal lobe epilepsy due to hippocampal sclerosis. Similarly, H.M.'s immediate auditory span was within normal limits (Milner, Corkin, & Teuber, 1968); Jeneson, Mauldin, and Squire (2010) studied others with mesial temporal damage and found they were able to maintain a small number of object-location associations over a short period of time. As with H.M., their performances fell off sharply with larger information sets, regardless of repeated learning trials. While participation of mesial temporal areas appears to occur "if the capacity of working memory is exceeded" (Jeneson & Squire, 2011), fMRI has demonstrated progressively diminished mesial temporal activity with increased working memory demands (Stretton et al., 2012).

Information held in working memory originates from both sensory input and long-term stores, dependent upon the task (Strauss, Sherman, & Spreen, 2006). A number of studies have described a direct relationship between long-term memory activation and working memory capacity (Cantor & Engle, 1993; Cantor, Engle, & Hamilton, 1991; Radvansky & Copeland, 2006; Unsworth, Brewer, & Spillers, 2013). Recent studies have implicated the hippocampus in coordination of neocortical regions for the purpose of re-activating internal representations during WM efforts (Poch & Campo, 2012). Synchronization of hippocampal and prefrontal areas has also been measured by coherence of rhythmic activity in rats while engaged in learning (Benchenane et al., 2010). These oscillations change depending upon the type of information being processed, and may have a role in working memory as well as long-term consolidation (Benchenane et al., 2011), particularly during slow wave sleep (Colgin, 2011).

The literature also presents evidence of extrahippocampal mesial temporal activity during working memory tasks. Egorov et al. (2002) found individual neurons in

the entorhinal cortex with the ability to generate graded persistent activity in response to consecutive stimuli. Theta oscillations in the entorhinal cortex correlate with working memory performance (Fransen, 2005) as they allow cells to maintain information for simultaneous computation or manipulation. The entorhinal cortex also appears to play a role in maintaining representations of stimuli with overlapping or ambiguous properties across short delay periods (Newmark, Schon, Ross, & Stern, 2013).

Temporal Lobe Epilepsy

Introduction to Epilepsy

Epilepsy is defined as a brain disorder characterized by a predisposition toward recurring, unprovoked seizures. It is the most common serious neurological disease seen in children (Friedman & Sharieff, 2006), affecting more than 345,000 children in the U.S. alone (Data Resource Center for Child and Adolescent Health, 2010), with much higher prevalence in developing countries (World Health Organization, 2016). Between 25 and 40 percent of patients do not respond adequately to pharmacological management and are thus considered to have refractory epilepsy (Kwan et al., 2010; Snead, 2001). Patients whose seizures originate from a focal area of the brain are especially at risk for pharmao-resistance (Donnadieu, 2013) but often benefit from surgical intervention (Foldvary, Bingaman, & Wyllie, 2001).

Lesional Substrates of Temporal Lobe Epilepsy

Focal seizures are usually classified into syndromes based upon the lobe in which they originate, although they may be caused by a variety of brain pathologies. Temporal lobe epilepsy (TLE) is the most common form of epilepsy (Devinsky, 2004) and is etiologically heterogeneous. Adult temporal seizures most commonly arise from acquired

damage to mesial temporal structures (Blumcke, 2009), while in children the basis may be either developmental or acquired postnatally. Focal cortical dysplasia (FCD) is one of most commonly identified developmental malformations associated with intractable pediatric epilepsy (Harvey, Cross, Shinnar, & Mathern, 2008; Cepeda et al., 2006), and is frequently associated with early seizure onset and neurological deficits (Chassoux et al., 2000). A high percentage of children with developmental malformations of the temporal neocortex have additional pathology of the hippocampus (Bocti et al., 2003; Mohamed et al., 2001).

***Focal Cortical Dysplasia*.** FCD is a developmental malformation of cortical brain tissue, identified by microscopic findings of disrupted laminar organization and abnormal neuronal morphology. While MRI findings typically include cortical thickening, blurring of the gray-white interface, and signal changes in the underlying white matter, FCD often remains undetected on MRI (Hader et al., 2004). FCD lesions are intrinsically epileptogenic (Boonyapisit et al., 2003; Morioka et al., 1999) often leading to high seizure burden (Bast, Ramanti, Seitz, & Rating, 2006). FCD as a cause of epilepsy was first recognized by Taylor four decades ago (Taylor & Falconer, 1971), when he reported cortical disorganization and large, bizarre-shaped cells in ten epileptic patients. Bocti et al. (2003) identified FCD as the cause of temporal lobe epilepsy in 64% of pediatric surgical cases evaluated.

Several groups have proposed classification systems specific to the focal cortical dysplasias. In 2004 Palmini et al. documented the consensus of an expert panel based on specific variants of neocortical architecture and cellular histopathology. Their taxonomy of FCD subtypes enabled more extensive study of histological correlation with clinical

variables. More recently, Blumcke and colleagues (2011) proposed an expansive classification system that includes occurrence of FCD in tandem with other brain lesions.

***Hippocampal Sclerosis*.** Hippocampal sclerosis (HS), also called mesial temporal sclerosis or Ammon's horn sclerosis, consists of neuronal loss, resultant atrophic change, and gliotic scarring. While the exact etiology is unknown (Thom, Zhou, Martinian, & Sisodiya, 2005), there is a strong association between febrile convulsions in childhood and the later observation of HS (Cendes et al., 1993). Despite lack of known causative mechanisms, animal models of damage to all hippocampal regions resulting from repeated kindled seizures suggest that HS is an acquired lesion (Cavazos, Das, & Sutula, 1994). HS further appears to be a progressive disorder, with greater severity of pathology associated with earlier onset and longer duration of seizures (Fuerst et al., 2001). Gradual decreases in hippocampal volume have been noted in patients with continued seizures (Fuerst et al., 2003), likely related to uncontrolled inflammation caused by a casade of molecular and cellular events associated with ongoing epileptiform discharges (Yang, Zhou, & Stefan, 2010).

Wyler and colleagues (1992) described a grading system for the progression of hippocampal sclerosis (based on relative gliosis and neuronal cell loss at pathology):

- Grade I: Mild damage to CA1, CA3, and/or CA4, with less than 10% neuronal loss
- Grade II: Moderate damage with 10 to 50% loss of neurons
- Grade III: Severe damage with more than 50% neuronal dropout, sparing CA2
- Grade IV: Marked mesial temporal damage, including greater than 50% cell loss involving all pyramidal cell layers. May also involve the dentate, subiculum, and parahippocampal gyrus.

More recently, an international consensus was reached that further refined HS subtypes based on specific areas of cell loss and gliosis (Blumcke et al., 2013).

MRI evidence of HS includes volumetric loss, increased T2 signal, and loss of normal internal architecture (Lewis, 2005). While MRI visibility often predicts that seizures will be pharmacologically resistant (Spooner, Berkovic, Mitchell, Wrennall, & Harvey, 2006), the severity of MR findings has not been directly correlated with intractability (Briellmann et al., 2007). Watson, Nielsen, Cobb, Burgerman, and Williamson (1996) devised a volumetric MRI grading system for HS, yielding high correlation with Wyler's pathological grades. This grading method is based upon comparison between the measured volume of the epileptogenic hippocampus and that of the non-involved side. Although such volumetric measurement requires manually defining structural contours due to the complexity of the hippocampal formation, it also allows pre-operative estimation of HS severity.

HS is the most common etiology of refractory seizure activity in adults (Lee & Lee, 2013). However, in children with TLE, HS is rarely found isolated from other pathologies (Mani, 2008). In a pediatric surgical series of 136 TLE patients aged 3 mos to 20 years, only 15% had HS (Wyllie et al., 1998). The majority of HS seen in childhood is in older adolescents, rather than younger children (Duchowny et al., 1992; Wyllie, 1998); while it does exist in younger children (Mohamed et al., 2001) the incidence in infants is rare (Mani, 2008).

***Dual Pathology*.** As implied by the label, "dual pathology" denotes the presence of more than one lesion type. For the purposes of this study, dual pathology designates only hippocampal sclerosis in tandem with FCD, consistent with type IIIa (Blumcke et

al., 2011). In most patients, the co-existing FCD is also located within the same temporal lobe as the HS (Fauser et al., 2006). In a minority of cases, signs of dysplastic tissue within the hippocampus itself have also been noted (Bocti et al., 2003).

Dual HS and FCD pathologies are frequently detected in epilepsy surgery patients, but the incidence varyies with population selection criteria. Overall studies of pediatric patients with temporal lobe epilepsy reveal dual pathology in 58 to 79 % of surgical patients (Bocti et al., 2003; Mohamed et al., 2001). Fifty-six percent of children and adolescents with histopathologically confirmed FCD evidenced dual pathology regardless of lobar location of dysplasia (Krsek et al., 2008). In children and adults with early seizure onset and confirmed FCD, 27% to 40% had co-occurring HS irrespective of seizure localization (Tassi et al., 2002; Fauser et al., 2006); in a similar sample using MRI evidence of FCD limited to the temporal lobes, this jumped to 87% (Ho, Kuzniecky, Gilliam, Faught, & Morawetz, 1998). In a surgical series of 33 adults with TLE, the majority had isolated HS, with only 48% evidencing dual pathologies (Eriksson, Nordborg, Rydenhag, & Malmgren, 2005).

Invasive EEG recordings have revealed patterns of epileptogenic activity associated with dual pathologies. In twelve children and young adults with temporal dual pathology seizure activity originating from the mesial temporal area in 41 % of the cases, 35 %t from the temporal neocortex, and 22 % demonstrated simultaneous discharges (Fauser & Schulze-Bonhage, 2006). Etiological theories of co-existing temporal pathology include kindling from the developmental malformation causing secondary damage to the hippocampal structures, and alternately, that both originate from a common developmental disturbance during gestation (Ho et al., 1998).

Cognitive and Psychological Considerations in Epilepsy

Cognitive deficits are frequently comorbid in children with epilepsy (Nolan, et al, 2003), particularly those with intractable seizures (Besag, 2006; Trimble, 1988). There is also a higher than normal incidence of learning disorders in this population (Beghi, Cornaggia, Grigeni, & Beghi, 2006; Lhatoo & Sander, 2001). TLE patients are at increased risk of impaired memory, language, and executive skills (Hermann et al., 2007; Laurent & Arzimanoglou, 2006). In most patients, these cognitive deficits are detectable at or before the onset of seizures (Helmstaedter & Kockelmann, 2006). While mental deficiencies are not universal to children with TLE, seizures beginning in childhood are associated with greater cognitive impairments than normal controls or patients with later onset (Hermann et al., 2002). The data suggest disruption of an early critical period of development by early seizure onset (Cormack et al., 2007; Glosser, Cole, French, Saykin, & Sperling, 1997; Korman et al., 2013). Cormack et al. (2007) reported that 82% of children with intractable temporal seizures that began prior to one year old had full-scale IQ scores below 79. While adult TLE is associated with a progressive decline in intellectual ability related to duration of the disease (Jokeit and Ebner, 1999; Marques et al, 2007; Oyegbile et al., 2004) pediatric studies have not demonstrated this relationship (Cormack et al., 2007; Korman et al., 2013).

Epilepsy also frequently has adverse impact upon quality of life and family adaptation (Leonard & George, 1999; Smith, Elliott, & Lach, 2004). In addition to obvious medical complexities, children with epilepsy have a high prevalence of comorbid psychiatric issues such as depression, anxiety, psychosis, and aggression (Grabowska-Grzyb, Jedrzejczak, Naganska, & Fiszer, 2006; Cornaggia, Beghi, Provenzi, & Beghi,

2006). Behavioral problems are also common (Austin et al., 2001; McDermott, Mani, & Krishnawami, 1995) including ADHD (Sherman, Slick, Connolly, and Eyrl, 2007) and social difficulties (Sugiyama et al., 1996), with considerably higher co-occurrence of autism than in the general population (Berg & Plioplys, 2012; Clarke et al., 2005).

Memory Deficits in Temporal Lobe Epilepsy

While seizures originating from anywhere in the brain can affect overall cognition, there are specific deficits associated with various focal lobar locations. TLE is associated with global cognitive deficits, but has its primary effect upon declarative memory (Guimaraes, Li, et al., 2007; Jocic-Jakubi & Jovic, 2006; Ozkara et al., 2004; Tudesco et al., 2010). In contrast, primary deficits in frontal epilepsy include psychomotor speed, attention, and immediate memory span (Helmstaedter, Kemper, & Elger, 1996). Nolan and colleagues (2004) compared memory performance in children with temporal lobe epilepsy, frontal lobe epilepsy, and childhood absence epilepsy. Their results indicated memory disturbance in all three groups, but patients with TLE had the highest risk of mnemonic deficits. Children with temporal lobe seizures demonstrated significant impairment in all verbal and most visual skills. Children with frontal lobe epilepsy were statistically below the norm for some of these tasks, while those with childhood absence seizures had only subtle deficits in visual memory.

A number of researchers have examined memory in patients with temporal lobe epilepsy (TLE). Most have found greater deficits associated with longer duration of epilepsy (Cheung, Chan, Chan, Lam, & Lam, 2006; Helmstaedter, Kurthen, Lux, Reuber, & Elger, 2003; Kent et al., 2006; Marques et al., 2007) and age of seizure onset (Alessio et al., 2004; Baxendale et al.,1998; Kent et al., 2006). Temporal lobe seizure activity is

associated with neuronal loss in the hippocampi and frontal cortex (Guimaraes, Bonilha, et al., 2007). While seizure frequency has been identified as a significant factor (Alessio et al., 2004), mnemonic impairments appear to result from a combination of transient ictal events and damage to neuronal structures (Helmstaedter & Kockelmann, 2006; Ozkara et al., 2004). Progressive memory impairments (Helmstaedter, Kurthen, Lux, Reuber, & Elger, 2003) are accompanied by reduced hippocampal fMRI activation during complex scene encoding in proportion to illness duration (Cheung et al., 2006). Declarative memory performance has been correlated to hippocampal volume as well as frontal lobe gray matter volume (Baxendale et al., 1998; Guimaraes, Bonilha, et al., 2007).

Certain patients with TLE may have normal performance on standard memory testing after a 30-minute delay, but deficient long-term retention, suggesting disruption of only long-term consolidation (Blake, Wroe, Breen, & McCarthy, 2000). Wilkinson et al. (2011) matched TLE patients to control subjects based on IQ, age, and gender. Compared with controls, patients with left sided HS demonstrated verbal memory deficits within a one-hour delay. Forgetting after six weeks was noted in patients with pathology on either side, and was related with seizure frequency. However, Bell (2006) found conflicting results with a different type of memory metric. Using retention scores, he demonstrated impaired performance for adults with TLE on WMS-III Logical Memory after the standard 30-minute delay, but after two weeks forgetting was proportional to controls. The utility of long-term retention testing in patients with TLE has not been substantiated, but these discrepant results do illustrate the importance of choosing proper measures and scoring methods.

Executive Deficits in Epilepsy

Impaired EF is a common finding in children with epilepsy, even when seizures are well-controlled (Parrish et al., 2007). Such deficits are found in localization-related as well as generalized epilepsy syndromes, but are notably worse in those with greater seizure burden (Treitz, Daum, Faustmann, & Haase, 2009). Children with recent-onset epilepsy have shown significantly greater EF deficits on parent ratings and objective testing compared with normal controls, even when seizures are well controlled (Parrish et al., 2007). In this population, executive skills are strongly related to quality of life (Sherman, Slick, & Eyrl, 2006). Children with frontal lobe epilepsy are particularly at risk for poor adaptive skills due to executive dysfunction (Culhane-Shelburne, Chapieski, Hiscock, & Glaze, 2002).

As expected, executive dysfunction often presents in patients with seizures originating in the frontal lobes. Many executive skills are subserved by a distributed network involving the frontal regions as well as other areas of the cortex (McDonald et al., 2006). Propagation of seizure activity to the frontal lobes by extrafrontal seizure activity is not uncommon (Stretton & Thompson, 2012). Indeed, executive deficits are also found in extrafrontal epilepsy (Treitz, Daum, Faustmann, & Haase, 2009), however there are notable localization-related and task-related differences (McDonald et al., 2005).

Rzezak and colleagues (2007) reported that children with temporal lobe epilepsy performed worse than controls on tests of semantic fluency, cognitive shifting, and forward digit repetition. Factors associated with poor EF included early age of seizure onset, years with seizures, and polypharmaceutical treatment. Those with mesial lesions

had worse overall executive performance than those with neocortical temporal lesions (Rzezak et al., 2007). Adults with mesial temporal seizures also performed worse than controls for risk-based decision-making based on feedback (Labudda et al., 2009). Several groups also found relative impairments on the Wisconsin Card Sort Test in TLE patients compared to neurologically normal controls (Kim, Lee, Yoo, Kang, & Lee, 2007; Martin et al., 2000; Wang et al., 2011). However, in contrast to pediatric studies associating mesial temporal foci with more impaired executive performance than lateral temporal foci, this was not a consistent finding across adults with TLE (Kim et al., 2007; Martin et al., 2000).

Cognition in Dual Pathology Patients

Only one report of neuropsychological performance in patients with dual-pathology was found in the literature. Martin, et al. (1999) studied fifteen adults with both HS and cortical dysplasia within the left temporal lobe and compared with HS-only patients. The majority of measures revealed no significant differences, however both groups showed impairments in verbal and visual memory, language skills, and academic achievement. Although verbal memory was equal overall, there was less efficient memory encoding in the dual pathology group, particularly with regard to utilization of semantic cueing to improve word list learning.

Research Hypothesis:

As illustrated by the preceding literature review, much has been learned about memory and hippocampal function, yet a great deal remains unknown. Based on this foundational knowledge, the following hypothesis was formulated to answer specific questions about hippocampal memory functioning and detection of dysfunction. Additional research questions arising in the process of data analysis are presented in the discussion.

Hypothesis: It was predicted that participants with dual pathology of the temporal lobe would have significantly worse memory performance than those participants with only neocortical pathology as measured by quotient of retained memory.

***Rationale for Hypothesis*:** Declarative memory differences between lateral and mesial substrates in adults have proven equivocal. Giovagnoli and Avanzini (1999) showed comparable levels of mnemonic deficit for lateral and mesial epileptic foci, while Jones-Gotman and colleagues (1997) demonstrated similar memory performance following resection of either hippocampus or temporal neocortex. Martin et al. (1999) found no overall difference in memory performance for patients with hippocampal sclerosis and those with additional neocortical malformations, but those with dual pathology did have less efficient encoding. Helmstaedter et al. (1997) indicated perhaps the most striking differences, with varying impairment patterns related to temporal lesion location. Findings have also varied in children. Although Gonzalez et al. (2007) revealed greater mnemonic deficits for mesial foci, Nolan and colleagues (2004) found no differences.

Because normative memory scores represent wholistic functioning of memory networks, including encoding, retention, and retrieval, these scores may be adversely

impacted by disruption to any part of the network (Jones-Gotman et al, 1997). This is exemplified in extra-temporal epilepsy syndromes (Jambaque et al., 1993; Lendt, Helmstaedter, & Elger, 1999) in which declarative memory impairments are found even in the absence of hippocampal dysfunction.

Compared with normative scores for delayed recall, the retention metric was expected to have greater statistical power to differentiate between TLE with and without hippocampal involvement. Normative scoring of delayed retrieval compares test subject performance against that of a sample of neurologically intact individuals within the same age group. In contrast, comparison of delayed memory performance to the subject's earlier performance mitigates potential effects of poor encoding in that individual (McDonald et al., 2001). Present knowledge of the hippocampal system and its presumed association with consolidation and retrieval of recently encoded information predicts that TLE that includes mesial temporal pathology would have significantly worse memory retention than TLE involving only neocortex.

An unpublished study of memory performance in pediatric epilepsy found retention scores discriminated between the presence and absence of hippocampal sclerosis, while normative delayed memory scores did not (Korman et al., 2010). However, selection criteria for that study included patients with seizures originating from various cortical regions and those with isolated hippocampal sclerosis, which were not included in the present study.

CHAPTER III: METHODS

Participant selection

Participants were retrospectively selected from a de-identified data set of patients with seizures resistant to anti-epileptic drug polytherapy who underwent surgical resection at Nicklaus Children's Hospital (NCH) from 1999 through 2015. All had been clinically referred for the treatment of intractable epilepsy and evaluated using a standardized presurgical protocol. Permission was obtained from the director of the NCH epilepsy program for use of surgical and neurological data, and the principle investigator has direct access to neuropsychological data through his employment at the hospital. Participants were chosen only if they met specific criteria for one of the study classifications, which included temporal lobe FCD, or dual pathology consisting of HS and FCD of the temporal lobe. A total of 54 subjects with EEG evidence of temporal seizure focus and histological diagnosis of temporal lobe FCD were chosen for inclusion; of these, 25 had FCD only, while the other 29 had dual pathology. Those with further pathology other than HS were excluded from the study, including tuberous sclerosis complex, brain tumors, polymicrogyria, nodular heterotopias, Sturge-Weber syndrome, and hemimegalencephaly. Potential participants with incomplete neuropsychological or clinical data were also excluded.

Participant Descriptives

Descriptive statistics are presented in table format to demonstrate basic information regarding participant data. General demographic information is presented in table 1, with descriptives for the entire sample shown in table 2.

Table 1:

Descriptive Statistics for Total Sample (N=54)

Characteristic	*Mean*	*Range*	*SD*
Age at Testing (years)	13.44	5.50-22.00	3.90
Age at Seizure Onset (years)	6.20	.10-16.00	4.50
Duration of Epilepsy (years)	7.38	1.0-15.56	3.90
Full Scale IQ	83.30	56-112	14.32
Verbal IQ	82.80	59-113	14.16
Performance IQ	87.70	55-130	16.67
Receptive Vocabulary	85.04	40-117	17.80
Final Learning Trial Raw Score	8.98	2-16	3.31
Learning Total Raw Score	27.91	7-45	8.85
Learning Total Scaled Score	7.46	2-14	2.46
Delayed Recall Raw Score	6.52	0-13	3.75
Delayed Recall Scaled Score	7.43	2-13	3.03

Of note, the mean full scale IQ for the entire sample was slightly more than one standard deviation below the normative population mean. The average delayed memory normative score was not quite a full standard deviation below the population mean.

Table 2:

Demographic Frequencies for Total Sample (N=54)

Characteristic	*n*	*%*
Gender		
Male	33	61.1
Female	21	38.9
Handedness		
Right	49	90.7
Left	5	9.3
Lesion Type		
FCD Only	25	46.3
Dual Pathology	29	53.7
Lesion Laterality		
Right	27	50.0
Left	27	50.0
Seizure Frequency		
Less than once per month	1	1.9
Monthly or more	8	14.8
Weekly or more	27	50.0
At least once per day	18	33.3
History of Status Epilepticus	12	22.2
Additional Frontal Lesion	5	9.3
Additional Parietal Lesion	4	7.4

Age at seizure onset was significantly correlated with Full-Scale IQ (r=.465, p<.01), with a stronger relationship to Verbal (r=.529, p<.01) than to Performance IQ (r=.329, p<.05). Demographic details are broken down by pathology type in table 3.

Table 3:

Descriptive Statistics for FCD Only and Dual Pathology Groups

	FCD Only (N=25)		Dual Pathology (N=29)			
Characteristic	*Mean*	*SD*	*Mean*	*SD*	*t(52)*	*p*
Age at Testing (years)	13.36	3.76	13.50	4.09	-.135	.893
Seizure Onset Age (years)	6.77	4.16	5.70	4.78	.870	.388
Epilepsy Duration (years)	6.75	3.43	7.91	4.24	-1.094	.279
Full Scale IQ	83.40	15.38	83.21	13.61	.049	.961
Verbal IQ	82.56	14.76	83.00	13.88	-.113	.911
Performance IQ	90.12	18.33	85.62	15.02	.991	.326
Receptive Vocabulary	86.08	21.28	84.14	14.49	.397	.693
Learning Total Raw Score	28.08	9.04	27.76	8.85	.132	.896
Learning Total Scaled Score	7.56	2.71	7.38	2.27	.266	.791
Delayed Recall Raw Score	6.84	3.59	6.24	3.92	.582	.563
Delayed Recall Scaled Score	7.48	2.82	7.38	3.25	.121	.904

Student's t-test revealed no statistically significant demographic differences between the two pathology groups for the characteristics presented in table 3. Additional descriptives broken down by pathology group are presented in table 4.

Table 4:

Demographic Frequencies for FCD Only and Dual Pathology Groups

Characteristic	FCD Only (N=25)		Dual Path (N=29)			
	n	*%*	*n*	*%*	χ^2	*p*
Gender					.930	.335
Male	17	68.0	16	55.2		
Female	8	32.0	13	44.8		
Handedness					4.75	.029
Right	25	100.0	24	82.8		
Left	0	0	5	17.2		
Lesion Laterality					.670	.413
Right	14	56.0	13	44.8		
Left	11	44.0	16	55.2		
Seizure Frequency					3.259	.353
Less than monthly	0	0	1	3.4		
Monthly or more	5	20.0	3	10.3		
Weekly or more	10	40.0	17	58.6		
At least once per day	10	40.0	8	27.6		
Status Epilepticus History	5	20.0	7	24.1	.133	.715
Additional Frontal Lesion	5	20.0	0	0	6.392	.011
Additional Parietal Lesion	3	12.0	1	3.4	1.432	.232

With the exception of handedness and presence of additional frontal lobe lesions, Chi-squared analyses indicated no demographic differences between the pathology

groups with HS (dual pathology) and without (FCD only). Left-handed participants were found exclusively in the dual pathology group (χ^2=4.750, *p*=.029); of the five, three had pathology of the left hemisphere, while the remaining two had right-sided lesions. Additional frontal lesions were present only in those participants without additional HS (χ^2=6.392, *p*=.011); only one had left hemisphere pathology, with the rest lateralized to the right side.

Measures

Neuropathological classification:

Brain tissue analysis on patients seen from 1999 to 2003 was performed at the Department of Pathology, Nicklaus Children's Hospital, Miami, Florida and for those seen from 2003 to 2013 it was done at the Department of Pathology and Laboratory Medicine (Neuropathology), David Geffen School of Medicine, University of California, Los Angeles. Inclusionary criteria were based upon pathology reported, as follows:

***Focal Cortical Dysplasia* (FCD)**. Determination of presence of FCD in both participants groups was based upon the histopathological classification system described by Palmini et al. (2004), as determined by histopathological findings from postsurgical pathology reports. Subsequent to 2004, reported findings were directly described as FCD, when applicable. For subjects that underwent surgery prior to 2004, histopathological findings that fit within FCD parameters were reclassified by the NCH epileptologists according to the Palmini et al. (2004) criteria: Architectural abnormalities and disorganization (e.g., laminar disruption, columnar disorganization), giant neurons, dysmorphic neurons, or balloon cells.

Dual Pathology. The presence of both FCD and HS was considered as dual pathology. HS was determined based on both histopathological and MRI criteria. Each potential participant for the dual pathology group was assessed for HS using findings from resected tissue and MRI evidence consisting of hippocampal atrophy, signal intensity change, and aberrant hippocampal architecture. In several cases, hippocampal specimens were fragmented and insufficient for histopathologic analysis, and the MRI data was used as the determinant of HS, as read/interpreted by an NCH neuroradiologist.

***Other lesional variables*:**

In addition to the histopathological classification obtained from resected lesions, other descriptive variables included the side of the lesion. When additional lobes were resected and contained FCD, those lobar locations were also recorded (e.g. frontal, parietal, occipital).

***Clinical variables*:**

As part of their presurgical evaluation, historical information was recorded for all participants and they underwent a neurological examination. Demographic variables recorded include gender, handedness, age at seizure onset, age at neuropsychological testing, frequency of seizures, duration of epilepsy prior to testing, and prior occurrence of status epilepticus.

Neuropsychological Variables:

Verbal Memory Assessment. The Wide Range Assessment of Memory and Learning (WRAML and WRAML2) is an instrument used for the evaluation of memory retention in many assessment contexts (Sheslow & Adams, 1990, 2003). The original WRAML was normed for children aged five through 17 years and is comprised of nine

subtests that yield three scales: Verbal Memory, Visual Memory, and Learning Scales. Four subtests also have delayed recall tasks. The WRAML2 extends the normative age range upward to 90 years and consists of six core subtests that factor into Verbal Memory, Visual Memory, and Attention/ Concentration. The newer version increased the number of delayed memory tasks to seven. The Verbal Learning subtest evaluates a child's ability to actively learn a list of non-related words and repeat as many as they can recall. This procedure was repeated for a total of four trials. Delayed Recall of the list was assessed after a delay of approximately 20 minutes to measure recall of previously learned verbal information. The same format, word list, and administration procedures are used for both WRAML editions: For children eight years and younger a 13-item list is used, while persons nine and older are given 16 items to learn. For this study, the raw scores for each learning trial and the delayed recall trial were obtained. The number of total words learned and later recalled after the delay were compared with age-based norms provided with the WRAML2 to yield a scaled score with a mean of ten and standard deviation of three. The WRAML2 norms were applied for all participants regardless of which version was originally used for testing.

***Assessment of Intellectual Ability*.** The Wechsler Scales of Intelligence were used to estimate intellectual functioning in all study participants. Wechsler Index Scores are presented as standard scores as described above. Full Scale IQ (FSIQ), a widely used marker of overall intellectual functioning, was used as a representation of participants' general cognitive ability. The specific test used depended upon age, the latest version available at testing, and clinical presentation. FSIQ scores between the tests used in this study are strongly correlated, with Pearson coefficients ranging from .84 to .94

(Wechsler, 1997; Wechsler, 2002; Wechsler, Coalson, & Riaford, 2008; Wechsler, Coalson, & Riaford, 2012).

Wechsler Intelligence Scales for Children- Third and Fourth Editions: The Wechsler Intelligence Scales for Children (WISC-III and WISC-IV) are individually administered instruments for assessing intellectual ability in children aged six years through 16 years, 11 months (Wechsler, 1991, 2003). They are each comprised of ten core subtests that represent specific domains of cognitive functioning, and provide a composite FSIQ score. The WISC additionally provides Verbal IQ and Performance IQ scores. The WISC-IV retained the majority of WISC-III subtests, and added five new tests. Index factors were structured to provide a Verbal Comprehension Index and Perceptual Reasoning Index that are clinically similar to Verbal IQ and Performance IQ. Additional, factor-based index scores are available with each WISC edition.

Wechsler Adult Intelligence Scales – Third and Fourth Editions: The Wechsler Adult Intelligence Scales (WAIS-III and WAIS-IV) are measures of intellectual ability for individuals aged 16 through late adulthood (Wechsler, 1997; Wechsler, Coalson, & Riaford, 2008). The WAIS-III has ten core subtests assessing various facets of intelligence that comprise the FSIQ, including: Picture Completion, Vocabulary, Coding, Similarities, Block Design, Arithmetic, Matrix Reasoning, Digit Span, Information, Picture Arrangement, and Comprehension. Subtest scores are combined to yield age-adjusted index scores, including FSIQ plus separate indices for Verbal IQ and Performance IQ. On the WAIS-IV Picture Completion and Comprehension are optional subtests, Picture Arrangement was deleted from the battery, with Symbol Search and Visual Puzzles added as core subtests required to calculate the FSIQ.

Wechsler Abbreviated Scales of Intelligence—First and Second Editions: The Wechsler Abbreviated Scales of Intelligence (WASI and WASI-II) are measures of intellectual functioning for individuals between 6 and 89 years of age (Wechsler, 1999; Wechsler & Zhou, 2011). They are comprised of four subtests as a means of quickly estimating intellectual functioning. The included tests are forms of those found in other Wechsler scales: Vocabulary, Block Design, Similarities, and Matrix Reasoning. These subtests were chosen for their association with general cognitive ability (g) and strong theoretical basis in intellectual measurement. The WASI yields three index scores: Verbal IQ, Performance IQ, and FSIQ. The WASI-II has the same basic structure as the earlier version, with updated psychometric properties.

Wechsler Preschool and Primary Scales of Intelligence- Third and Fourth Editions: The Wechsler Preschool and Primary Scale of Intelligence- Third Edition (WPPSI-III) is an instrument used to assess intellectual functioning in children aged 2 years, 6 months through 7 years, 3 months (Wechsler, 2002). In children older than four, seven core subtests that represent various domains (Block Design, Information, Matrix Reasoning, Vocabulary, Picture Concepts, Word Reasoning, Coding) are used to obtain age-adjusted index scores for FSIQ, Verbal IQ, and Performance IQ. For the WPPSI-IV (Wechsler, Coalson, & Riaford, 2012), the upper age norms were extended to 7 years, 7 months. Some subtests were deleted from the earlier version and others added. Only six subtests are needed to calculate the WPPSI-IV FSIQ in children four years and older: Block Design, Information, Matrix Reasoning, Bug Search, Picture Memory, and Similarities.

Procedures

Because this was a retrospective study, all data had been previously collected, including history, clinical information, and pathological analysis of resected tissue. Data resided in the NCH Department of Neurology and the NCH Brain Institute, Neuropsychology Section. Participant neurological, neuropsychological, and historical data were harvested from the NCH files by the principle investigator with permission of the hospital, and he personally entered them into an SPSS data table for study analyses. Neuropsychological measures were administered to patients by licensed clinical neuropsychologists or doctoral-level practicum students or interns trained and supervised by a licensed neuropsychologist in the NCH Brain Institute.

Since this study involved archival data, exempt status was secured from the Western Institutional Review Board (WIRB), the body representing Nicklaus Children's Hospital. Approval and exempt status was subsequently obtained from the Nova Southeastern Institutional Review Board. In keeping with IRB requirements and standards for the protection of human subjects, all collected data used for analyses were devoid of protected health information and de-identified to maintain the confidentiality of participants.

CHAPTER IV: RESULTS

Preliminary Analyses

All data analyses were conducted using IBM's SPSS version 24. Prior to analyses, data tables were visually evaluated for missing and extreme values to ensure fidelity of data entry. Following this, descriptive values were examined to determine that scores fell within the actual range of values for each measure recorded. Continuous variables were also analyzed for departures from normality that might limit statistical inference, including skewness and kurtosis statistics, as presented in table 5.

Table 5.

Normality Statistics for the Entire Sample (n=54)

			Shapiro-Wilk	
Variable	Skewness	Kurtosis	Statistic	*p*
Retention Quotient	.431	2.700	.929	.003
Final learning Trial	-.330	-.427	.965	.111
Highest Learning Trial	-.202	-.475	.966	.130
Total Learning Raw Score	-.284	-.392	.979	.462
Words recalled after delay	.001	-1.098	.957	.051
Delayed memory scaled score	.008	-1.073	.955	.040

All continuous variables had normal skew, with delayed recall raw and scaled scores at the upper limits of normality for kurtosis; the retention quotient was noted to be significantly leptokurtic, thus violating standards of normality. The failure of these variables to fall within a normal distribution was not entirely surprising due to the

relatively small number of patients in the sample. Although not all properties of population samples are normally distributed, most tend toward a normal distribution as the sample size increases (Sirkin, 1999). Kurtosis is especially dependent upon the scores in the tails of a distribution, to a greater extent than scores in the center of the distribution. Although there were no "extreme" values for the recall measures (raw and scaled scores), scores were distributed across the range, giving a boxy appearance to the distribution and increasing the kurtosis statistic.

Table 6 presents normality statistics broken down by pathology group.

Table 6.

Normality Statistics Broken Down by Pathology (FCD= Focal Cortical Dysplasia; DP= Dual Pathology)

Variable	Pathology	n	Skewness	Kurtosis	Shapiro-Wilk
Retention Quotient	FCD	25	1.288	4.608	.881**
	DP	29	-.523	.170	.939
Final Learning Trial	FCD	25	-.794	-.477	.885**
	DP	29	.161	.087	.967
Highest Learning Trial	FCD	25	-.601	-.818	.907*
	DP	29	.170	.219	.961
Learning Total Raw	FCD	25	-.660	-.174	.954
	DP	29	.037	-.368	.973
Words recalled after delay	FCD	25	-.035	-1.258	.946
	DP	29	.062	-1.009	.938
Delayed Memory Sc. Score	FCD	25	.169	-1.095	.938
	DP	29	-.070	-1.120	.945
Age	FCD	25	.092	-.571	.972
	DP	29	-.276	-.471	.961

*p< .05 **p < .01

As expected, there was some additional non-normality found after separation into groups due to diminished sample sizes. However there was also an emerging trend noted whereby the learning scores showed more negative skew in the FCD group and greater positive skew in the dual pathology group.

Study Analyses

***Hypothesis*:** It was predicted that participants with dual pathology of the temporal lobe would have significantly worse memory performance than those participants with only neocortical pathology (FCD) as measured by quotient of retained memory.

Statistical Approach: The hypothesis was tested using a two-way mixed design ANOVA incorporating both between-subject and within-subject analyses and their interactions. Side of lesion was included as an independent variable, since verbal memory measures have previously shown association with the left hemisphere. The within-subject factor was the difference across time between initial word learning (e.g., final learning trial, previously the denominator of the retention quotient) and delayed word recall (previously the numerator of the retention quotient). The two between subject factors were type of pathology and side of pathology. Although certain variables in the model did not meet strict ANOVA normality assumptions, the F-test is robust enough to withstand minor deviations from normality while preserving the Type I error rate (Schmider, Ziegler, Danay, Beyer, & Buhner, 2010; Zar, 1996), and there was no violation of variance homogeneity.

Table 7 indicates the means and standard deviations for memory measures relevant to the hypothesis, broken down by type of pathology and hemispheric laterality.

Table 7.

Memory Variable Means and Standard Deviations by Pathology Type and Side

	Type of Pathology			
	FCD Only (n=25)		Dual Pathology (n=29)	
Memory Variable	*M*	*SD*	*M*	*SD*
Retention Quotient	.776	.362	.672	.333
Words Recalled After Delay	6.84	3.59	6.24	3.92
Final learning Trial	9.20	3.55	8.79	3.14

Table 8 represents a summary of ANOVA results for the main hypothesis.

Table 8.

Main and Interaction Effects for Mixed Design ANOVA Comparing Final Learning Trial with Words Recalled After a Delay

Source	*df*	*SS*	*MS*	*F*	*p*	η^2
			Within Subjects			
Memory	1	165.42	165.42	52.29	.000	.511
Memory* Path	1	.094	.094	.030	.864	.001
Memory* Side	1	2.35	2.35	.741	.393	.015
Memory *Path*Side	1	3.34	3.34	1.057	.309	.021
Within Subjects Error	50	158.17	3.16			
			Between Subjects			
Pathology Type	1	7.77	7.77	.372	.545	.007
Side of Lesion	1	.988	.988	.047	.829	.001
Pathology*Side	1	110.76	110.76	5.309	.025	.096
Between Subjects Error	50	1043.16	20.86			

These analyses demonstrated a significant main effect for memory scores, indicating a statistically significant difference between the mean number of words learned on the final trail and those recalled following a delay period. Inspection of the scores revealed that as expected, word recall after a delay was lower than at the end of the learning trials, dropping by approximately 2.5 words on average across the entire sample. While between-subjects analyses demonstrated a significant interaction between type of pathology, side of lesion, and the mean of the two memory scores, they did not indicate significant interaction between pathology type, side of lesion, and the within-subject main effect between final learning trial and delayed recall. Thus, the proposed hypothesis was not supported. To isolate the source of the significant interaction effects, exploratory analyses were performed using univariate ANOVAs. Pathology type and lesion laterality were the predictors, with final learning trial and words recalled after delay analyzed individually as dependent variables. Results are presented in Table 9.

Table 9.

Exploratory ANOVA Results for Interaction Between Pathology Type and Lesion Laterality, by Final Learning Trial and Delayed Recall (Independently)

Source	*df*	*SS*	*MS*	*F*	*p*	η^2
DV: Final Learning Trial						
Pathology Type (Path)	1	3.07	3.07	.307	.582	.006
Side of Lesion (Side)	1	3.19	3.19	.318	.575	.006
Path * Side	1	76.30	76.30	7.61	.008	.132
Error	50	501.20	10.02			
DV: Delayed Word Recall						
Pathology Type (Path)	1	4.79	4.79	.342	.561	.007
Side of Lesion (Side)	1	.145	145	.010	.919	.000
Path * Side	1	37.81	37.81	2.70	.107	051
Error	50	700.14	14.00			

As indicated in table 9, the exploratory ANOVA's revealed that the interaction between pathology type and side of lesion was significantly associated only with final learning trial and not with delayed recall. Additional follow-up t-tests comparing mean final learning trial scores for each type of pathology by side are shown in table 10.

Table 10.

Post-hoc Comparison of Final Learning Trial Means by Pathology for Each Side

	Type of Pathology								
	FCD Only			Dual Pathology					
Side	*n*	*M*	*SD*	*n*	*M*	*SD*	*t(25)*	*p*	*Cohen's d*
Left	11	10.82	2.04	16	7.94	2.32	3.322	.003	1.33
Right	14	7.93	4.01	13	9.85	3.76	-1.279	.213	.51

Comparison of final learning trial means by pathology for each side of lesion using Student's t-test revealed significant differences between pathology groups, but only for lesions occurring on the left side. As expected, the mean difference showed better learning in the group without hippocampal sclerosis, with a large effect size (Cohen's d = 1.33). Although the proposed hypothesis was not supported, the data did demonstrate that pathology of the left hippocampus has a significant relationship with diminished verbal learning rather than with memory retention.

A-Posteriori Analyses

The means and standard deviations for additional memory measures of interest are shown in table 11, by pathology grouping and side of lesion, along with exploratory significance testing for differences between pathology group means.

Table 11.

Additional Memory Variable Means, Standard Deviations, and Test of Differences by Pathology Type and Side

Memory Variable	Side	Type of Pathology: FCD Only *n*	FCD Only *M*	FCD Only *SD*	Dual Pathology *n*	Dual Pathology *M*	Dual Pathology *SD*	*t*
Words Recalled	Total	25	6.84	3.59	29	6.24	3.92	.582
After Delay	Right	14	6.14	3.51	13	7.23	4.53	-.701
	Left	11	7.73	3.66	16	5.44	3.27	1.704
Delayed Mem	Total	25	7.48	2.82	29	7.38	3.25	.121
Scaled Score	Right	14	7.21	2.52	13	8.08	3.50	-.740
	Left	11	7.82	3.25	16	6.81	3.02	.825
Final Learning	Total	25	9.20	3.55	29	8.79	3.14	.447
Trial	Right	14	7.93	4.01	13	9.85	3.76	-1.279
	Left	11	10.82	2.04	16	7.94	2.32	3.322**
Highest	Total	25	9.48	3.10	29	9.17	2.92	.376
Learning Trial	Right	14	8.43	3.44	13	10.23	3.22	-1.40
	Left	11	10.82	2.04	16	8.31	2.41	2.815**
Total Learning	Total	25	28.08	9.04	29	27.76	8.85	.132
Raw	Right	14	25.79	10.40	13	30.77	9.97	-1.269
	Left	11	31.00	6.23	16	25.31	7.24	2.120*
Total Learning	Total	25	7.56	2.71	29	7.38	2.27	.266
Scaled Score	Right	14	7.57	3.18	13	8.15	2.58	-.520
	Left	11	7.55	2.12	16	6.75	1.84	1.038

*$p < .05$ **$p < .01$

Although delayed recall scores showed no contrast between the pathology groups with and without hippocampal involvement, each of the non-normative variables related to verbal learning (Final learning trial, high learning trial, raw total learning) did show significant differences between pathology groups, but only for those with left-sided pathology. The difference between pathology groups was in the direction expected for all three learning scores, with the group having hippocampal disease demonstrating the worse performance.

Binomial logistic regression was performed to determine how well participants with left-sided pathology were classified by pathology type, based on final learning trial. Categorization accuracy is represented in table 12.

Table 12.

Classification of Predicted vs. Actual Pathology Type, for Left-Sided Pathology Only

Actual Group Membership	*n*	Predicted Group Membership			
		Dual Pathology		FCD Only	
		n	*%*	*n*	*%*
Dual Pathology	16	13	81.3	3	18.7
FCD Only	11	4	36.4	7	63.6

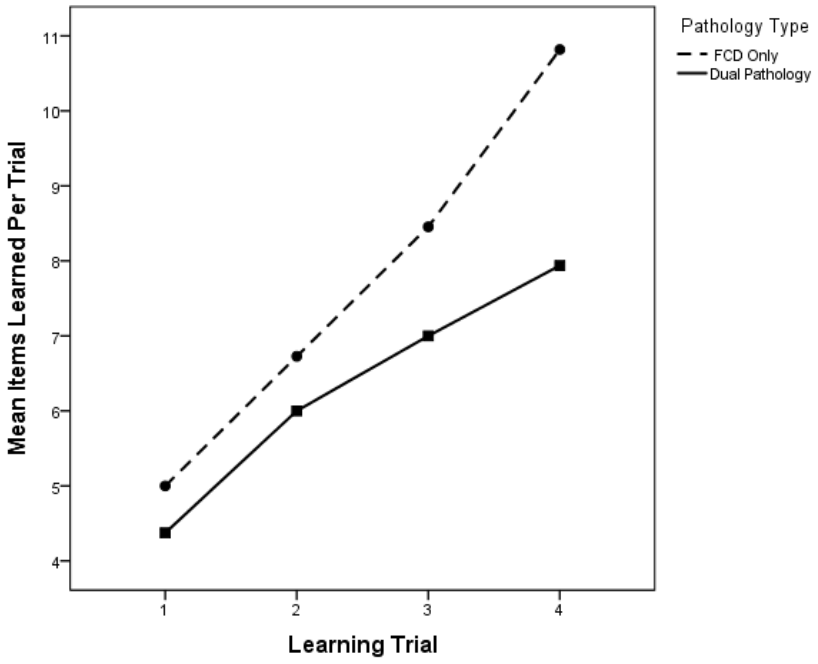
Note: Overall percentage of correctly classified cases= 74.1

Although more than 81% of the dual pathology group were correctly classified based on final learning trial, just under 64% of the FCD group were placed in the correct category.

A visual representation of learning trial means for participants with left-sided pathology is presented in figure 2.

Figure 2.

Mean Learning Trial Performance by Group, Only Left Temporal Lesions



While the number of words repeated during the initial two trials demonstrated no significant difference, there is increasing divergence noted as the trials proceed, with much better performance for the group without hippocampal pathology by trials three and four.

Table 13 presents additional breakdown of language measures by side of pathology.

Table 13.

Means, Standard Deviations and Test of Differences for Language Measures by Side, Broken Down by Pathology Type

Language		Side of Lesion							
		Left			Right				
Variable	Pathology	*n*	*M*	*SD*	*n*	*M*	*SD*	*t*	*p*
Verbal IQ	FCD	11	83.55	16.14	14	81.79	14.15	-2.90	.774
	Dual Path	16	83.31	14.30	13	82.62	13.91	-.132	.896
PPVT	FCD	11	81.64	22.95	14	89.57	20.03	.923	.366
	Dual Path	16	85.25	13.65	13	82.77	15.91	-.452	.655

As shown in the table above, there were no significant lateralized differences between language tasks, regardless of pathology.

To determine whether having left-handed participants or those with additional frontal lobe pathology changed the relationship between the final learning trial and pathology type, additional exploratory analyses were run. Table 14 presents a summary of ANOVA results without including data points for those participants that are left handed and for those with additional frontal pathology.

Table 14.

Exploratory ANOVA Results for Interaction Between Pathology Type and Side upon Final Learning Trial, with Specified Participants Excluded

Source	*df*	*SS*	*MS*	*F*	*p*	η^2
			Left- Handers Excluded			
Pathology Type (Path)	1	5.91	5.91	.625	.433	.014
Side of Lesion (Side)	1	8.69	8.69	.919	.343	.020
Path * Side	1	50.55	50.55	5.34	.025	.106
Error	45	425.67	9.46			
			Additional Frontal Lobe Pathology Excluded			
Pathology Type (Path)	1	3.67	3.67	.385	.538	.008
Side of Lesion (Side)	1	.451	.451	.047	.829	.001
Path * Side	1	52.19	52.19	5.47	.024	.108
Error	45	429.13	9.54			

Table 15 indicates the means and standard deviations for the memory variables entered into the analysis without the inclusion of participants having additional frontal pathology, broken down by laterality and type of pathology.

Table 15.

Final Learning Trial Mean and Standard Deviations Excluding Specified Participants, with Significance Testing by Pathology Type

	Type of Pathology								
	FCD Only			Dual Pathology					
Side	*n*	*M*	*SD*	*n*	*M*	*SD*	*t*	*p*	*Cohen's d*
Left- Handers Excluded									
Left	11	10.82	2.04	13	8.08	1.98	3.335	.003	1.42
Right	14	7.93	4.01	11	9.27	3.58	-.871	.393	-.364
Additional Frontal Lobe Pathology Excluded									
Left	10	10.60	2.01	16	7.94	2.32	2.987	.006	1.22
Right	10	8.30	3.97	13	9.85	3.76	-.954	.351	-.416

Despite exclusion of each of these subsets of participants, the difference between pathology groups for the final learning trial continued to be statistically significant, with robust effect sizes only for those with left hemisphere involvement. Thus, the mean difference between pathology groups on the left side continued to show better learning in the group without hippocampal sclerosis.

Chapter V: DISCUSSION

The purpose of the current study was to gain a greater understanding of the relationship between neuroanatomical memory structures and functional determinants of their cognitive and psychophysiological properties. This process has been approached through exploring alternate application of conventional memory indices, with a subgoal of identifying hippocampal damage in children with intractable seizures originating from the temporal lobe through measures of verbal learning and retrieval.

Discussion of Study Results

The study hypothesis predicted that memory retention, as measured between the last learning/encoding trial to delayed recall of the list of stimuli on a word list learning test, could differentiate those participants having only neocortical pathology from those with dual pathology of the temporal lobe. The expectation was that pathology involving hippocampal structures would be associated with far greater loss of encoded verbal information than pathology that did not involve the hippocampus. While the data did not support this hypothetical relationship, the findings have potentially important implications and raise many relevant questions.

This study was somewhat unique in that both groups had underlying focal cortical dysplasia affecting the temporal neocortex. One of the groups had additional damage to the mesial temporal region, predominantly affecting the hippocampus. Thus, the two pathology groups had overlapping, yet neuroanatomically distinct involvement of the temporal lobes, as confirmed by post-surgical microscopic evaluation of resected tissues. Because both sets had developmentally-based disruption of cortex and seizures that were pharmacologically intractable, similarities between the groups (i.e., seizures, medication

effects, developmental issues) helped to reduce or eliminate biases that might have otherwise occurred if comparing epileptic patients with neurologically normal controls. In this regard, the FCD group functioned as a clinical control against which participants in the dual pathology group could be contrasted.

Based on the results of the present study alone the data demonstrated a significant role of left hippocampus in the encoding phase of verbal memory. In addition to association of left mesial temporal networks with the final word learning trial, there was a distinction between specific neuroanatomical components of the memory system, but only within the dominant hemisphere. When group scores for children with HS were contrasted with others having very similar features except that they lacked HS, a robust inter-group difference emerged with large effect size.

Because the final learning trial was significant only for lesions on the left side, classification of predicted vs. actual pathology type was run only for those participants with left-sided epilepsy. Classification into each pathology type had an overall accuracy of 74 percent; sensitivity for the detection of HS was 81 percent, while the specificity was only 64 percent. Thus, the prediction rate for presence of hippocampal pathology was much better than for that of its absence (e.g., FCD only). Based on these data, if the final learning trial is used independently of collateral information, there is a much higher probability of accurately predicting the presence of hippocampal pathology than its absence.

Additional exploratory analyses showed that among the learning scores collected, the fourth learning trial, high learning trial (defined as the higher of the third or fourth learning trials), and raw total for all trials each demonstrated a statistically significant

association with left temporal hippocampal pathology. However the earlier learning trials revealed no relationship with pathology type. As expected, the total learning score had a smaller effect size than either the high or final trials, due to mathematical dilution by the early trials. The finding that only later trials are of significance in predicting pathology type suggests the importance of one or more properties of incremental learning across trials with regard to hippocampal function. Visualization of the learning slopes for both groups, as illustrated in figure 2, reveals that the slope for the FCD group, in which both hippocampi have remained intact, initially parallels that of the group with left hippocampal damage, but the slopes begin to diverge after trial two and become increasingly disparate by the final trial.

Examination of the mean scores across each learning trial for participants with left-sided pathology revealed that FCD group mean scores were higher than the dual pathology group across all learning trials. These differences were relatively small and insignificant for the first two trials and became incrementally larger, with the biggest discrepancy on the final learning trial. The mean scores themselves, which represent the number of words correctly repeated on each trial, also increased incrementally across trials for both pathology groups. However, a comparison of differences between the final and high learning trials for left-sided lesions revealed only a small disparity between these scores within each pathology group, consistent with the significant association of pathology type and each of these learning metrics.

Taken together, the data indicate that the hippocampus shares the task of learning verbal stimuli across repetitions with working memory systems. On early trials, where there are few words learned, working memory carries the load independently, but as the

stimulus burden increases, the intact language-dominant hippocampus progressively contributes to enhancement of cumulative learning. Mesial temporal structures do not autonomously support verbal learning until the buffer for immediate auditory memory reaches its capacity. In this situation, repetition is necessary to raise the quantity of learned stimuli high enough to saturate the buffer. In the present sample the buffer's capacity was estimated to be about seven to eight words.

Results of the within-subjects ANOVA also revealed a main effect of memory whereby the scores decreased in the interval between learning and recall for the entire group. Inspection of the mean standard scores for total learning and delayed recall for the current sample reveal that the standard scores are nearly identical across the time points, reflecting that the change across time is in the direction expected and already accounted for by the WRAML norms. More importantly, there was no interaction between the within-subject main effect of memory and pathology group. Therefore, although there was a statistically significant loss of information from learning/encoding to recall, it is not substantively important because of symmetrical performance across pathology groups when pathology when considering participants with damage on both sides of the brain.

As with most measures of cognition, verbal memory tests reflect functions across a widespread cognitive network, with proper performance requiring integrated activity of multiple cognitive and neurological functions (i.e., attention, hearing, language). Therefore, resultant scores represent synchronous performance of the function of interest along with numerous ancillary processes. Assuming adequate support from other cognitive systems, memory scores that are below normative expectancy represent the potential failure of any one of a number of components or connections within the

eloquent network. This principle is well-represented by overall memory measures for the present sample, as indicated in the demographics. Across the entire sample, the mean for delayed recall scaled scores are nearly one standard deviation below that of the normative population, with virtually identical scaled scores across both pathology groups for both total learning and delayed memory. This is a good indicator of the WRAML Verbal Learning subtest's ability to detect global memory dysfunction; however, using the traditional indices of immediate and delayed recall, these scores lack neuroanatomical specificity.

Cognitive reserve is a concept most commonly applied to aging and dementia, but potentially applicable to temporal epilepsy. Simply put, cognitive reserve provides a buffer against cognitive decline, despite underlying pathological degradation of neuronal systems. Although learning scores produced a strong effect for differentiating between pathology types at the group level, they are not reliable at the individual level. Various reserve mechanisms offer possible explanations for why learning scores may not be a direct reflection of hippocampal disease, despite strong statistical association. For the current study the following mechanisms may have occurred either individually or in some combination: (1) enough neuronal substrate remained viable to support adequate recall, (2) cognitive networks underwent offsetting plastic changes, or (3) more dynamic compensatory mechanisms were able to perform the task normally handled by the damaged hippocampal formation.

When both hippocampi are destroyed by pathology or surgical removal, a dense amnesia is inevitable. In unilateral HS however, gradual, progressive degradation of affected structures may allow relative maintenance of function for some time. As neurons

within Ammons Horn regions slowly die and the hippocampus visibly shrinks, the pathological threshold will eventually be reached, at which point memory scores would be expected to fall. However, when the contralateral hippocampus remains intact, as with all study participants in the dual pathology group, homologous structures may compensate and maintain memory function. However, this is also likely to depend upon mediation by the intact contralateral hippocampus.

In the current study, another potential source of memory reserve is assistance from semantic memory. In general, learning is supported by anchoring new information to the base of existing semantic knowledge. Stronger reservoirs of factual information, vocabulary, and general word knowledge commonly bolster performance when learning an unfamiliar list of words through semantic priming. Because semantic memory stores consist of information most often learned in school (i.e., factual knowledge and information about the world), they are highly correlated with educational attainment, a common proxy for cognitive reserve.

Given that verbal memory was being measured, the interaction between pathology type and side of the lesion was not unexpected. The results also add conceptual meaning to the debate regarding the side of mesial temporal dysfunction in relation to memory modality. Verbal memory measures lateralize to the left hemisphere due to the match between characteristics of the stimuli and those of the left-sided cortical structures. Verbal stimuli are consistently processed by the left hemisphere when they have been previously encountered, with greatest reliability for overlearned stimuli. The left hemisphere is also more likely to process concrete details, especially those that are familiar. In addition to meeting the aforementioned criteria, stimulus words would also be

processed by the left hemisphere due to their linguistic qualities. In the current sample, participants with left-sided temporal lesions did not perform any worse than those with right-sided lesions for measures of verbal functioning that include Verbal IQ and receptive vocabulary. Furthermore, neither of the verbal measures differentiated between pathology types in participants with left-sided lesions. It is therefore accepted that the verbal learning task is measuring primarily mnemonic rather than linguistic performance, as related to pathology type.

The final learning trial can be useful for discrimination between pathology types for those participants having left-sided lesions due to the interaction between the side of lesion and type of pathology that allows for differentiation based on learning performance. However, these findings do not generalize to performance of modal-specific memory tasks (i.e. verbal vs. visual tasks) based on hemispheric side. This means that memory performance in children is not expected to be a good predictor of epileptogenic zone lateralization, regardless of whether verbal or nonverbal memory is being measured.

Alterated or atypical language networks are common among the epilepsy population and may play a role in memory performance because of affiliations between mesial and lateral temporal structures. When considering the importance of propositional language lateralization, the high rate of left-handed subjects within the sample becomes a salient demographic issue. Of the total sample of 54 participants, the five members (9%) identified as left-handed were all in the dual-pathology group (17% of that group), much higher than expected rates by all accounts. Of these five left-handers, three had left-sided temporal seizure onset, which tends to cause re-organization of language networks to the

contralateral side. Assuming all three had atypical, right-sided language networks, this would pose no threat to increased type I error. To determine whether this might have an effect upon study outcome, the five left-handed participants were removed from the data set and analyses run again, without a substantial difference in outcome.

Likewise, as indicated in the demographics, five participants had additional frontal lesions detected during their neurological workup, all from the FCD group. Among these, only one had left-sided pathology, while the remaining four had seizures emanating from the right hemisphere. After exclusion of these frontal lobe cases from the data set, additional analyses were performed, which showed that these cases of additional frontal pathology also had negligible effect on the study results.

Although semantic and episodic memory are psychophysiological constructs that do not necessarily coincide with anatomical brain regions, such paradigms are often defined by how they are measured. Logically, tests purported to measure explicit memory have been assumed to measure processes related to mesial temporal structures, and likewise, hippocampal functioning is generally considered a dimension of episodic memory. Because current results indicate that hippocampal functioning has a significant relationship with learning (perhaps better described as ‘progressive encoding across trials’), consideration of how verbal learning paradigms fit within the contemporary memory taxonomy is warranted; this in turn leads to questions regarding the relationship between memory theory and clinical reality. Do these tasks qualify as being valid appraisals of episodic memory, semantic memory, or something different altogether? Regardless of labels, what processes are the tasks actually measuring? Contrasted with memory for logical passages, learning and recall of simple stimuli (e.g., word lists) lacks

contextual information such as time, place, or emotional frame of reference; therefore, such tasks do not capture 'episodes' in the traditional sense of the construct, and certainly not in the same manner as story memory. Such learning and recall of serial information results in encoded information devoid of episodic tags such as "who, why, when, and where," falling short of reaching the episodic benchmark. On the other hand, stimulus word lists do provide an indication of "what" but words by themselves do not constitute facts, concepts, or other meaningful information about the world; thus, learning and recall tasks of this type also do not meet criteria for semantic memory measures.

With this in mind, it may be appropriate to consider whether the current taxonomy of declarative memory is a suitable conceptual framework on which to base the next generation of mnemonic research. In particular, the role of item context and its potential impact upon functional localization of neuroanatomical correlates should be carefully deliberated.

General Discussion

Within the neurosciences, evaluation of deficits specific to mesial temporal lobe dysfunction has presented as a major challenge (Rausch, 2002). Although many contemporary memory measures appear to be sensitive to global memory dysfunction, they lack neuroanatomical specificity and are not valid differentiators between types of memory disorders (Delis, Massman, Butters, & Salmon, 1991). While attempts to improve verbal learning tasks by adding metrics for monitoring memory strategies and errors have aided our understanding of memory processes, they have not improved neuroanatomical relevance.

A number of promising studies conducted in the 1990's suggested that beyond identification of generalized dysfunction of the network, certain verbal memory scores could be useful for measuring hippocampal function in adults with temporal lobe epilepsy. In particular, significant associations were noted between the percentage of information retained from logical passages and MRI-based measurements of the language-dominant hippocampus, both before and after surgical resection. In left TLE, Wechsler Memory Scale (WMS) Logical Memory retention has been correlated with presurgical hippocampal volumes (Lencz et al., 1992) and with residual volumes after resection (Trenerry et al., 1993).

Sass and colleagues (1992b) described recall of logical story passages relative to initial learning as a means of identifying left mesial hippocampal disease in adults with temporal epilepsy. They stated that "when patients can be equated with regard to their initial level of performance on measures of story recall, measurement of the loss of information over time is sensitive to hippocampal dysfunction." Their group further identified percent retention of Logical Memory on the WMS as an indicator specific to left hippocampal disease (Sass et al., 1992b), with presurgical retention scores correlating with histopathological analysis of hippocampal cell loss following surgery (Sass et al., 1992a). Moreover, immediate and delayed recall scores by themselves failed to differentiate between mesial and lateral temporal lobe pathology. Another group found similar results with story retention, but only in patients with bilateral atrophy of the hippocampal structures (Sawrie et al., 2001). However, despite the evidence correlating story memory retention with hippocampal pathology, this may have been an effect of measuring language more than memory skills. To wit: The Boston Naming Test, a

measure of confrontational naming and language ability, was noted to independently correlate with hippocampal pathology (Sass et al., 1992b), suggesting that story memory's sensitivity to left hippocampal dysfunction may vary with language competence.

Correlational studies between list learning and story memory measures have indicated strong convergence across their primary indices (Delis, Cullum, Butters, & Cairns, 1988). For the current study, the decision to adapt the retention quotient to a verbal learning paradigm rather than story memory for isolating hippocampal pathology in children was based on factors believed to make the former more suitable for this particular application. First was data suggesting that word list memory is more sensitive than story memory for detecting mesial temporal pathology. This included a study of older Korean adults that described superior discrimination between neurological normals and those with Alzheimer's pathology (Baek, Kim, & Kim, 2012). Thus, even in other languages and cultures, verbal learning tests appear to be more sensitive than story memory. Secondly, many children with intractable seizures have impaired language skills, particularly those with dominant temporal lobe epileptogenic zones, and may struggle with accurate story recall due to the high burden imposed on language skills (Sass et al., 1992a; 1992b). The word list task was expected to be less dependent upon language competence. Use of the retention quotient was further intended to eliminate personal biases in encoding that might affect retrieval by comparing information recall with the participant's own prior performance.

Numerous studies have evaluated mesial temporal functions in patients with Alzheimer's dementia (AD) and amnestic mild cognitive impairment (MCI). AD is a

progressive disease that primarily affects older adults, beginning in the perirhinal and entorhinal regions of the mesial temporal lobes, progressively spreading to the hippocampus, and ultimately to neocortical regions (Braak & Braak, 1995). Meanwhile, MCI is considered a prodromal phase of AD that demonstrates similar patterns of hippocampal subfield atrophy (Mueller et al., 2010). Because of the high correlation between hippocampal volume and general memory performance (Bonner-Jackson, Mahmoud, Miller, & Banks, 2015; Kilpatrick et al., 1997) it comes as no surprise that people with AD have greater memory issues than their neurologically normal counterparts (Barnes et al., 2009).

The current study has shown a relationship between hippocampal disease and learning scores in children with temporal lobe epilepsy. This is consistent with a report by Kockelmann et al. (2006) indicating that verbal learning is subserved by the left hippocampus, particularly the dentate gyrus, CA3, and CA4 regions. Atrophy of the mesial temporal structures has likewise been correlated with diminished learning performance in amnestic MCI (Gifford et al., 2015), while a number of studies have also indicated that learning can discriminate between patients with AD and controls. Specifically, multiple authors have demonstrated worse learning across trials for AD or MCI patients than in and elderly neurological controls (Delis, Massman, Butters, & Salmon, 1991; Mast & Allaire, 2006; Foster et al., 2009; Woodard, Dunlosky & Salthouse, 1999). Furthermore, hippocampal responsivity to fMRI during learning tasks may successfully differentiate AD patients from controls (Johnson et al., 2008). Abnormalities of hippocampal development secondary to prenatal alcohol exposure have

been associated with impaired verbal learning in children (Willoughby, Sheard, Nash, & Rovet, 2008).

The hippocampal learning effect may depend, at least in part, on stimulus familiarization across repeated trials. In a study of adults with AD, Wolk and Dickerson (2011) observed that only the final learning trial correlated with MTL atrophy, while earlier learning trials did not. This was reinforced by a more recent study indicating that discriminant power may be improved by increasing the number of learning trials presented (Wang, Li, Li, & Zhang, 2013). Taken together, these findings are consistent with the suggestion made by Hermann, Wyler, Bush, and Tabatabai (1992) that mesial temporal structures play an important role in learning when the capacity of the short-term memory buffer has been exceeded. Extrapolating from Miller‘s work (1956) to supraspan learning tasks, hippocampal activation may be necessary to support encoding beyond about seven words (“plus or minus two”); this is consistent with present data but might expected to be lower for younger or more impaired children. Indeed, with bilateral hippocampal damage, HM was able to flawlessly repeat six digit strings, but regardless of the number of learning trials could not remember any additional digits (Jeneson, Mauldin, & Squire, 2010).

Although well-accepted that individuals with hippocampal damage are prone to memory impairments, diminished performance on global memory measures may also be caused by damage or disease within various other neuroanatomical regions (Zola-Morgan & Squire, 1993). Episodic memory may be compromised by selective damage either to mesial temporal structures or the surrounding Papez network (Dickerson & Eichenbaum, 2010). Not only is there no singular site or cortical circuit that can independently

subserve episodic memory functions, but neuroanatomical locations or connectivity may also vary with specific task characteristics (Rugg, Otten, & Henson, 2002).

Functional neuroimaging, and fMRI in particular, has played an invaluable role in understanding brain connectivity and plasticity. Performance-based imaging studies continue to be the primary means of delineating functional networks that are task or action-dependent. There is evidence that declarative memory in healthy individuals activates a network that includes not only the perirhinal and entorhinal cortices, hippocampus, and amygdala, but also the lateral temporal neocortex (Gour et al., 2011). This suggests that abnormalities of lateral temporal cortex, such as FCD, have the potential to substantially impact explicit memory functions. It also helps make sense of studies demonstrating that some verbal memory impairments may stem from ether mesial or lateral temporal disturbance. Furthermore, temporal lobe epilepsies commonly present with altered connectivity of memory network components proximal to the seizure onset zone. Within the hemisphere of the epileptogenic focus, fMRI has further demonstrated diminished connectivity between the posterior cingulate gyrus and the hippocampus, as well as between the hippocampal formation and the parahippocampal cortex (James, Tripathi, Ojemann, Gross, & Drane, 2013).

Adding to the complexity of understanding eloquent functional networks, in patients with early onset epilepsies, connectivity and network development are subject to plastic changes, particular when seizures are present during nascent maturational stages. Because TLE is a systemic brain disorder, abnormal physiological alterations are generally accompanied by numerous pathophysiological changes to cognitive networks that extend far beyond the seizure onset zone. Left TLE with HS is notable for white

matter alterations within the ipsilateral temporal lobe, as well as connections to mesial temporal, bilateral frontal, and parietal areas (Liu, Chen, Beaulieu, & Gross, 2014; Voets et al., 2009). Network changes include both increased and reduced connectivity. While functional coupling may decrease between some areas of the affected temporal lobe and homologous regions in the opposite hemisphere, frontal and subcortical connectivity may be enhanced (Maccotta et al., 2013). TLE patients have shown negatively correlated connectivity maps in comparison with controls (Morgan, Gore, & Abou-Khalil, 2010). Noted changes to cortical hubs include gray matter atrophy in temporal, frontal, and parahippocampal areas, as well as in the cerebellum (Riederer et al., 2008).

While the neocortex is material specific, mesial temporal areas are regarded as being relatively nonspecific, with the left hippocampus involved in processing verbal memory only because of its interaction with neighboring neocortical structures (Helmstaedter et al., 1997). Patients with bilateral hippocampal damage or surgical removal suffer permanent episodic memory loss (Milner, 2005; Scoville & Milner, 1957). When considering postoperative changes following unilateral hippocampal resection, most studies have found that the degree of memory decline following surgery is greatest in those with the best memory performance (LoGalbo et al., 2005; Stroup et al., 2003). Intact memory is directly related to the least amount of compromise to hippocampal neurons. Because HS is a progressive, slowing evolving condition, the drop in memory performance is essentially the result of resecting residual hippocampal tissue that has remained functional (Fuerst et al., 2001; Rausch & Babb, 1993; Helmstaedter, Elger, Hufnagel, Zenter, & Schramm, 1996; Witt et al., 2015). Two studies have demonstrated learning and memory declines following resection in children with left temporal seizures,

with the majority recovering by one year after surgery, regardless of pathology (Gleissner et al., 2002; Gleissner, Sassen, Schramm, Elger, & Helmstaedter, 2005). Adults evidenced similar declines, but did not show recovery as the children had.

Given the high rate of atypical organization of language networks in patients with left temporal lobe epilepsy, language lateralization can potentially confound the evaluation of unilateral hippocampal functioning. A considerable number of children with left TLE show atypical language organization prior to surgery (Korman, 2010; Maulisova et al., 2016); however, declines in verbal episodic memory immediately following left hippocampectomy reflect that at the time of surgery right mesial temporal structures had not yet subsumed verbal memory functions. Many adults with left temporal lobe epilepsy also exhibit atypical language organization (Powell et al., 2007), even though they do not recover verbal memory after hippocampal resection, regardless of how much time has elapsed since surgery. This is presumably due to adults having less residual developmental plasticity than children. Thus, despite early reorganization of language networks, it appears that memory network restructuring ensues only after many months following mesial temporal surgery in children, but not in adults. Verbal memory is not necessarily isolated to one hemisphere, but functional contributions to verbal learning and memory are best evaluated within the context of lesions affecting the language-dominant hemisphere. However, modal-specific memory weakness is not necessarily a reliable indicator of epileptogenic zone lateralization.

The concept of memory reserve capacity as it relates to epilepsy has been described in a handful of studies. As with the dementia studies, higher levels of reserve have been associated with better preservation of overall cognitive functioning in epileptic

adults (Jokeit & Ebner, 1999; Oyegbile et al., 2004; Pai & Tsai, 2005). Studies and reviews focused on memory resilience specific to temporal lobe epilepsy have discussed various factors related to viability of diseased structures, plasticity of memory networks, and degree of compensation by contralateral structures (assuming they are intact) following resection (Chelune, 1995; Helmstaedter,1999).

Semantic and episodic memory likely rely on different networks, yet are functionally interrelated, affecting each other at encoding as well as retrieval (Greenberg & Verfaellie, 2010). Whether or not the hippocampus participates in semantic consolidation and retrieval remains a topic of ongoing debate. While retrieval of existing semantic knowledge is relatively unaffected by bilateral hippocampal damage (Schmolck, Kensinger, Corkin, & Squire, 2002), fMRI activation of the left hippocampus has been observed during both episodic and semantic retrieval (Ryan, Cox, Hayes, & Nadel, 2008). In a study of children with temporal lobe epilepsy, Smith and Lah (2011) found a double-dissociation between scores for semantic and episodic memory tasks. Some children performed well on semantic but not on episodic memory tasks, whereas others had poor episodic performance, but scored well on semantic tasks. Their results suggested two neuroanatomically distinct systems, with episodic memory subserved by mesial temporal systems while semantic memory is instead reliant on lateral structures. Other authors have postulated that semantic information is initially acquired as episodic, but over time aspects of the episode fade away, including the time of acquisition and information source (Cermak, 1984; Moskovitch et al, 2005.)

The hippocampus appears to improve semantic competence in neurologically normal individuals, but evidence suggests that the hippocampus is not absolutely

necessary for acquisition of semantic knowledge. While semantic learning is impaired following mesial temporal damage, factual knowledge can still be augmented by other intact brain regions (Kensinger & Giovanello, 2005; Vargha-Khadem et al., 1997). This was exemplified by the ability of amnestic patients including H.M. (Corkin, 2002; O'Kane, Kensinger, & Corkin, 2004) and others (Manns, Hopkins, & Squire, 2003) to make semantic knowledge gains, although the process is quite slow, laborious, and inefficient.

Semantic memory may also function in a priming capacity for episodic memory (McNamara, 2005). In neurologically intact individuals, factual knowledge stores may act as a framework for encoding of episodic information (Brewer & Treyens, 1981). Strong foundational knowledge of a particular subject tends to aid episodic learning and recall for related details (Schneider, Korkel, & Weinert, 1989). In contrast to H.M. and others who were unable to augment episodic knowledge, some amnestic patients with mesial temporal damage have been able to support new episodic learning using semantic information as anchor or reference points (Kan, Alexander, & Verfaellie, 2009). Taken together, these semantic-episodic interactions suggest a compensatory mechanism whereby levels of functionality are maintained in spite of underlying pathology, providing a reserve capacity of sorts. In a similar vein, procedural and declarative memory processes may also interact to optimize performance, even though they are clearly anatomically distinct systems (Poldrack & Rodriguez, 2004).

The most common demographic characteristics used to estimate cognitive reserve have included years of education (Stern, 1992) and IQ (Stern, 2009), particularly premorbid IQ levels (Alexander, 1997). Given that semantic knowledge capacity, a form

of crystallized intelligence, is often used to estimate premorbid IQ, it is a likely candidate as a CR proxy (D'Aniello, Castelnuovo, & Scarpina, 2015). Semantic memory impairment is often noted in patients with AD, but generally only after substantial progression of pathology (Hodges & Patterson, 1995) due to failure of explicit retrieval mechanisms (Rogers & Friedman, 2008). Until that point is reached, semantic knowledge may bolster explicit memory performance and maintain apparent function.

In formulating the hypothesis for this study, prior research describing the mnemonic roles of medial and lateral temporal structures was carefully considered. The adult epilepsy literature reported that temporal neocortical structures mediate working memory (Helmstaedter et al., 1997) and material-specific acquisition, including verbal learning (Helmstaedter et al., 2008). Numerous authors have also indicated that the mesial temporal structures support long-term retrieval and consolidation of episodic memory (Harand et al., 2012; Hosscheidt, Nadel, Payne, & Ryan, 2010; Rutishauser, Schuman, & Mamelak, 2008). This study derives alternative concepts of hippocampal involvement in verbal memory, with the implication that memory systems are considerably more complex than often described using the current theoretical framework.

Limitations

Various limitations of this study warrant discussion so they may be addressed in future investigations. While retrospective studies have certain advantages, they often present with numerous challenges, particularly when taking information collected within a clinical context and configuring it to answer a set of research questions. Because of the archival nature of this study, some usable data fields were limited across subjects. This was largely due to the clinical practice of tailoring measures used and scores collected to

fit demographic requirements and respond to individualized referral questions. Moreover, some subjects had to be systematically excluded due to missing data points. This effect was further amplified by the collection of information across multiple years. Over any expanse of time, not only do new versions of tests and new measures emerge, but there may be shifts in the zeitgeist that dictate which tests are the most appropriate for any given clinical presentation.

There are also far more limitations in pediatric than adult practice. When working with children, the measures used vary depending upon age, with fewer available tests for younger children. Measures of memory begin at age five and are very simplistic. Executive skills are not effectively measured until about age 7, when reading skills become proficient enough to produce reliable responses to written and more language-laden tasks. Thus, it is often not possible to use equivalent measures across a broad range of pediatric ages. Because children with early onset epilepsy tend to be lower functioning, evaluation of this group poses additional challenges. Compared with the general population of refractory pediatric epilepsy, the present study sample is likely biased toward somewhat higher functioning children, only because they were able to complete most of the neuropsychological measures presented. Despite this upward bias, the mean full scale IQ for the entire sample of study participants was still just under one standard deviation below the normative population mean. Validity of memory scores may also be confounded by the attentional and behavioral difficulties often seen in children with epilepsy.

Because sampling bias can affect results, a discussion of specific factors leading to this type of bias is warranted. Since microscopic examination of tissue is required to

verify pathology, the accuracy can occasionally be confounded by technical issues. This can be especially problematic for certain hippocampal resections in which structures are removed using vacuum extraction, rather than being taken out en-bloc; this may lead to small or insufficient amounts of tissue available for evaluation, perhaps not representative of the entire specimen. Hippocampal subfield damage to may differentially influence memory performance depending upon the specific areas affected (Coras et al., 2014). Pathological grading is also more difficult when surgical specimens are damaged during surgical removal. Specimen characteristics can also bias the pathological analysis if not all sectors are not represented (e.g., isolated anterior hippocampus). Fortunately, most bias can be reduced through specialized staining techniques that delinate mossy fiber sprouting, which increases with hippocampal damage and is a sensitive and reliable measure of HS progression, regardless of the section sampled (Proper et al., 2001). The use of radiological scales for grading the progression of hippocampal sclerosis can provide secondary evidence of hippocampal status (Watson et al., 1996), which would likely improve diagnostic accuracy for research as well as clinical applications.

Presurgical neuropsychological assessment is often complicated by the passage of time between seizure onset and evaluation, which may be a number of years in some cases. During this time period, the brain may compensate through reorganization of networks and the child may either compensate behaviorally or other behavioral issues may arise, which in turn can interfere with the evaluative process. Because the early onset of seizures tends to interfere with neurocognitive development and critical periods, older children who have an extended seizure history may be exceptionally delayed or difficult

to test, particularly when considering the sparse selection of age-appropriate measures with very low psychometric floors.

When doing research involving hippocampal sclerosis, it is often easier to work with adult patients than children. Because HS generally develops later in life, there are considerably greater numbers of adult than child cases without additional cortical pathology. Having a larger base population increases the ease of recruiting and retaining study populations. Most adults have also had the opportunity to develop normally prior to disease onset, contrasted with pediatric populations that are often very cognitively impaired due to developmental interference and similar complexities. Regardless of the intended clinical or research application, developmental differences must be accounted for in the assessment of , it is not feasible to compare raw scores across subjects of different ages, or even those at different developmental levels. Thus, despite showing a strong relationship between hippocampal dysfunction and repetitive learning trials, raw learning scores are meaningless in isolation. Without having a normal group against which to compare, we only know that patients with left hippocampal damage tend to have worse learning than those with FCD. However, we don't yet have information on how patients with lateral temporal lobe damage (e.g., FCD group) compare against age-matched, non-neurological patients. Normative memory scores from the current sample suggest that patients with lateral temporal pathology have general memory issues equal in magnitude to those with unilateral mesial temporal pathology. Furthermore, stratification by age, laterality, and lesional variables may prove challenging, particularly when studying children, in whom underlying lesions rarely affect a single cortical lobe.

As new neuropsychological techniques are developed and older applications refined, accompanying changes in knowledge or understanding are likely to require new terminology or a new application of meaning to existing terms to accurately describe phenomenon and maintain scientific consistency. In the current study, there is only a vague definition of what constitutes "learning, " which makes it more difficult to interpret the relevance of the findings. In this case, learning is defined more by what is measured, and less through theoretical construct, which also creates ambiguity for terminology associated with learning and memory and the relationship between the two. Furthermore, although the terms have been used somewhat interchangeably, it is hardly clear whether learning is the same as memory encoding, or perhaps one is a subset of the other. This becomes problematic, as previously explained, because the use of a retention index relies entirely on knowing how much information was actually encoded. Otherwise, deficient encoding could masquerade as poor recall. This might be resolved through the use of an immediate recall trial following the completion of learning trials, which could then be compared with the recall after a delay period, such as presented on the CVLT. Although an interference trial (e.g., given on the CVLT following immediate recall) may indicate resistance to decay and intrusion, it is likely to again confound the discernment of what has actually been encoded versus what is retained. Thus, it is important to plan for the memory properties of interest and carefully choosing the specific tasks that will achieve that goal. However, this also means that memory measures cannot be "all things to all neuropsychologists" and poses a considerable challenge to test developers.

Analysis of the data presented some challenges due to limited sample size, which diminished the statistical power to differentiate between groups. Although there was a

large effect size for the relationship between final learning trial and hippocampal function, the fewer subjects means that results may be less reliable than with a larger group. There were also some departures from normality that violated basic assumptions of parametric statistics, some of which stemmed from the relatively small number of subjects. This became more of an issue when groups were broken down by hemispheric laterality and even more when divided into pathology type. Alternative ways of performing statistical analyses were used when possible, such as using a repeated measures ANOVA, rather than analyzing the retention quotient, due to high kurtosis in the latter composite variable. Although there were no true outliers, some distributions had more high and low scores than expected. This particularly affected word recall following the delay for the entire sample (both the raw score and associated scaled scores) due to squared-off distributions stemming from scores in the tails of the distributions. When variables were broken down by pathology group, even more examples of non-normality were observed, affecting the final and highest learning trials. Because this often happens as sample sizes become smaller, it was not unexpected. Inspection of skewness statistics and histogram plots revealed significantly accentuated negative skew for the group of participants with FCD only upon these learning variables, consistent with the analytic data previously presented.

Future Directions

Although the data did not directly support the hypothesis as predicted, it did raise a number of relevant questions for further exploration that will presently be addressed.

Perhaps most importantly, the results indicate that currently available memory tests are good at quantifying overall memory competence, but yield very little

information relevant to anatomical localization. Although neurologists and neurosurgeons now rely on MRI and other advanced imaging procedures to determine the location of brain tumors, the neuropsychologist is still heavily relied upon to provide information upon which decisions will be made about surgical procedures. This is especially true for those involving hippocampal resection or ablation. With the discovery of a new way of using and interpreting an old measure as a starting point, new tests need to be developed that provide a normative basis of comparison, rather than needing to compare clinical cases as referential controls.

However, before new tests are developed, the present results should be replicated and tested within a broader scope to ensure that there is a true relationship between learning and hippocampal function. Pediatric replication should be done across stratified age cohorts. To rule out potential developmental confounds, testing with adults is also warranted, which would also ensure that results may be generalized across age groups. Because FCD is an unusual finding in adults, those with HS would likely need to be compared with non-neurological controls.

While expected that learning across trials as a marker of left hippocampal dysfunction should be robust across various verbal learning measures, this will remain uncertain until further studies are done. The strength of the effect is also likely to vary, depending upon stimulus and test-specific characteristics such as list length and word properties that include imageability, semantic relation, and base rate frequency of natural occurrence. Several examples illustrate the importance of stimulus selection upon learning. Task demands vary with different lengths of word lists, which can in turn affect how information is processed (Sunderaramon, Blumen, DeMatteo, Apa, & Cosentino,

2013). Learning across trials has demonstrated significant correlation between the Hopkins Verbal Learning Test (HVLT) and the California Verbal Learning Test (CVLT) within groups of normal elderly as well as patients with AD (Lacritz & Cullum, 1998; Lacritz, Cullum, Weiner, & Rosenberg, 2001). However these studies showed little association between the learning tasks for certain error types and recognition scores.

Surprisingly, there is not a large body of literature discussing the effects of implicit semantic structure within memory tasks. Categorical groups of words within a list (such as found on the CVLT) might improve encoding through a chunking strategy that effectively reduces the number of individual elements (McLean & Gregg, 1967). As long as subjects know the basis for category membership (i.e., peaches and grapes belong to the fruit category) memory processes become more efficient by freeing up working memory and requiring less hippocampal activation during encoding. However, this does not necessarily improve encoding in healthy young adults (Shear, Wells, & Brock, 2000). Despite enhanced semantic clustering during delayed recall on the CVLT, overall recollection was not superior to participants who did not receive semantic cueing prior to stimulus presentation. Furthermore, the implicit structure of the CVLT may even diminish sensitivity to some deficits in impaired patients. A study comparing the CVLT-C with WRAML verbal learning in children within the fetal alcohol spectrum found significantly better delayed retention on the semantically structured measure, while these differences were not present in age-matched healthy controls (Roebuck-Spencer & Mattson, 2004). Results indicated that less-structured tests like the WRAML were more sensitive to deficits in memory retention, suggesting that word list structure may actually mask certain types of deficits rather than revealing them.

Finally, standard administration procedures for most memory measures include similar delay times to that used in the present study. Because recall after a 20 minute delay was not related to hippocampal function, future studies should evaluate recall at varying time intervals to validate this finding or determine the condition(s) under which the hippocampus does participate in memory recall. Delay times should be strategically created, with suggested intervals at one hour, one day, and one week; it is acknowledged that the longer intervals will be more difficult to test, however technology now makes it possible to test long memory delays through remote means (i.e., telephone and internet-mediated video chats). Randt, Brown, and Osborne (1980) developed an adult memory test with 24-hour delay norms intended to be tested remotely by telephone, but this practice has not been incorporated into any contemporary memory measures. While the delay between word list presentation and "long term" recall is routinely evaluated after a 20 to 30 minute delay interval (Delis, Kramer, Kaplan, & Ober, 1994; Schmidt, 1996; Sherman, E.M., & Brooks, 2015), this interval appears to be arbitrarily set. While the present results indicate that this time period allows for the normally expected decay of information there was no evidence discovered in the literature or test manuals for determination of this epoch. Thus, additional study is required to determine the most appropriate recall delay times for memory measures, particularly for evaluation of those patients with potential mesial temporal damage.

Drawing upon the present results, we can speculate that a nonverbal learning analogue presented across four trials might yield similar results for the opposite hemisphere. However, numerous caveats would need to be addressed before conclusions regarding the role of hippocampal function could be generalized across learning

modalities. Although the use of nonverbal stimuli may intuitively make more sense from the standpoint of eliminating language as a source of potential confound, the following issues are likely to be encountered in this endeavor: First, although the right hemisphere may process a visual gestalt, more concrete, familiar details within the design are less likely to reliably lateralize to the right side. Secondly, nonverbal stimuli may be prone to automatic verbal labeling, dependent upon complexity, novelty, and other characteristics, thereby further confounding results. Furthermore, due to the nature of verbal stimuli and overlearning, words are likely to be automatically processed by the left hemisphere, but there is no prepotent analogue for the right hemisphere and processing of nonverbal stimuli. As has been found previously, there are fewer lateralizing effects for non-verbal than verbal memory (Alessio et al., 2006; Baxendale et al., 1998; Bonilha et al., 2007; Sawrie, et al., 2001), suggesting greater difficulty in isolating non-language-dominant hippocampal function in participants with intact contralateral structures.

Because the results of this study and the work of other authors have suggested that repeated learning across multiple trials is a key element for the hippocampus to participate in learning, further study of this phenomenon is warranted to elucidate the key elements and specific processes involved. Consideration should be given to the learning slope, as that has been identified as an indicator of material specific memory impairments in temporal lobe epilepsy (Foster, et al., 2009). Other studies in epileptic patients have correlated left temporal resections with reduced verbal learning slope (Dulay et al., 2009). Others have suggested that learning slope may represent a neurophysiological process associated with the hippocampal formation (Poreh, Sultan, & Levin, 2012).

Despite such mentions in the literature, there is little published empirical evidence validating a relationship between hippocampal functioning and rate of stimulus learning.

The effect of the number of learning trials is also worthy of consideration. The current data further suggest that a minimum of four consecutive repetitions is necessary to engage the hippocampus enough to find group differences in children. The difference in words learned between trials three and four was a sensitive differentiator between subjects with and without hippocampal dysfunction, and this juncture also appeared to be when the hippocampal structures assumed primary control of the encoding process. It is vital to recognize that the current paradigm identified participants with HS due to failed activation of the hippocampus across progressive learning trials, while those with intact hippocampi had relatively enhanced encoding in the later trials, but were less-successfully identified. Within this context it would be helpful to know whether additional trials might improve specificity enough to differentiate between pathologies at an individual level. While overall memory screening may be sufficient with few encoding trials, measure suitability depends on the intended use. This is also important because some abbreviated learning tasks, such as that found in the Child and Adolescent Memory Profile (ChAMP) with only three verbal learning trials (Sherman & Brooks, 2015) may not sufficiently evaluate for memory issues isolated to elements of the Papez circuit.

Finally, if future studies do validate learning scores as a gateway to identification of hippocampal damage, then more practical applications may be devised and tested. One of the most germane uses would be for improving the prediction rate of relative risk and degree of verbal memory decline following left hippocampal resection. In patients with intractable seizures it may be used in conjunction with imaging and electrophysiological

data to help identify the presence and extent of hippocampal dysfunction prior to surgery. With further development that includes well thought-out study designs and the inclusion of appropriate control subjects to improve specificity rates, outcome studies will ultimately determine whether this may one day be successfully applied to the prediction of individual outcomes.

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