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Assessing Verbal Memory Task Performance and Intractable Epilepsy: The Associations among Hippocampal Volume Ratio, Seizure Demographic Factors and Memory Indices

Alexis Gabrielle Burks

Alexis Gabrielle Burks

Candidate

Psychology

Department

This thesis is approved, and it is acceptable in quality and form for publication:

Approved by the Thesis Committee:

Steven P. Verney, Chairperson

Lynette Abrams-Silva

Ben Clark

Bradley Lega

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Alexis G. Burks

B.S., University of Texas at Dallas, 2014

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By

Alexis G. Burks

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M.S., University of New Mexico, 2023

Abstract

Epilepsy affects 3.4 million people in the United States and may affect their memory performance. This study investigated the relationships between memory performance, hippocampal volume ratio, and demographic factors in adults with intractable epilepsy in standardized memory tasks and an experimental memory task designed to be repeated daily. Participants underwent electrode implantation surgery and completed comprehensive neuropsychological assessments prior to surgery including an experimental memory task during their stay in the hospital. Correlation, ANOVA, and regression analyses were completed. The standardized memory tasks and the experimental memory task were significantly correlated. Hippocampal volume ratio was not significantly correlated to memory performance nor was seizure onset zone in these analyses. Regression analyses

showed no significant relationship between hippocampal volume ratio, verbal memory performance, and demographic factors. Further analysis is needed to better understand these relationships and the utility of the experimental repeatable memory task, improving clinical outcomes in epilepsy.

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Introduction

Epilepsy is a disorder characterized by seizure activity in the brain, affecting 3.4 million people in the United States, or 1.2% of the population, and 70 million globally (*Epilepsy Data and Statistics | CDC*, 2020; Thijs et al., 2019). Within the United States, the vast majority, approximately 3 million, of those affected are adults. There is no notable gender difference in rates of epilepsy, however emerging research suggests that secondary impact of antiepileptic medication may be more common in women (Christensen et al., 2005; Luef & Taubøll, 2015). Epilepsy is a unique disease as it can be idiopathic, having no known cause, or pathogenic. For those with pathogenic epilepsy, the leading causes are stroke, traumatic brain injury, central nervous system infection, and perinatal risk factors (*Epilepsy Data and Statistics | CDC*, 2020). Roughly 60 percent of individuals with epilepsy have idiopathic epilepsy. Epilepsy onset has a bimodal distribution, tending to onset in childhood or over the age of 60 (Holmes, 2012; Kotsopoulos et al., 2002). Approximately one third of patients with epilepsy have intractable epilepsy, epilepsy that doesn't respond to medication (Sinha & Siddiqui, 2011). In the United States, the direct cost of epilepsy is approximately $28 million a year (*Examining the Economic Impact and Implications of Epilepsy*, n.d.).

Many people with epilepsy are unable to work and many people go untreated despite the diagnosis, especially in low-income countries (Saxena & Li, 2017). Globally, there are major treatment gaps and inequities with 80% of those with epilepsy living in low- or middle-income countries (Saxena & Li, 2017). Additionally, there are both within and between country treatment gaps, even though the cost of treatment can be as low as five US dollars a day (*Examining the Economic Impact and Implications of Epilepsy*, n.d.). Within the United Stated, racial/ethnic disparities persist as well. Kroner (2013) found that in a

major metropolitan area the overall rate of epilepsy was 1.53%, similar to the national rate. However, non-Hispanic whites had a lower rate of 0.77% while African Americans had a much higher rate of 2.13% (Kroner et al., 2013). Kroner also found that the prevalence rate was higher in low-income homes (2.27%) and those with less than a high school diploma (3.4%) (Kroner et al., 2013).

Because of the nature of the disorder and its complexity, it is often associated with a host of neurobiological, psychological, and cognitive problems (Fisher et al., 2014; Thijs et al., 2019). Those with epilepsy are more likely to experience depression, anxiety, and psychosis than the general population, with 20% having a diagnosis of generalized anxiety disorder (*Mental Health*, n.d.). Additionally, prevalence rates of depression in patients with epilepsy are 20 to 50 percent and patients with epilepsy are at increased risk for suicidality (Alsaadi et al., 2015). In 2017, an estimated 17. 3 million adults, about 7.1% of the adult population, had at least one depressive episode (*NIMH » Major Depression*, n.d.-a). Indicating that rates of depression are higher in individuals with epilepsy than the general population. Patients with depression have been shown to have cognitive impairments in executive functioning, attention, and memory (Hammar, 2009). Executive functioning difficulties, specifically inhibition, problem solving, mental flexibility, verbal fluency, decision making, and working memory, have been seen in the acute phase of major depressive disorder (MDD) (Hammar, 2009). Effortful attention and processing speed are often impaired in patients with MDD (Hammar, 2009; Marazziti et al., 2010). There have been variable reports of memory deficits in depression, with some studies reporting no difference between controls and depressed patients and other studies reporting memory deficits in depressed patients (Elliott, 1998).

Cognitive impairment such as memory and attention issues, are common with epilepsy and are often exacerbated by antiepileptic medication (Park & Kwon, 2008). Memory difficulties are a common experience for individuals living with epilepsy, however the mechanisms underlying these difficulties are not well known (William Barr, PhD, ABPP, 2014). Memory impairment also largely contributes to poor quality of life for individuals with epilepsy (Reed, 2019). Specifically, verbal memory deficits are very common in patients with temporal lobe epilepsy, the most common type of focal epilepsy, epilepsy that originates at a specific area of the brain (*Epilepsy Data and Statistics | CDC*, 2020; Reed, 2019). Mayeux found that temporal lobe epilepsy may be associated with anomia, an aphasia where names of objects are forgotten (Mayeux et al., 1980). More recently, temporal lobe epilepsy has been associated with other adverse effects to cognition, like declines in verbal fluency and naming abilities (Thompson & Duncan, 2005). This study investigates verbal learning and memory performance in adults with intractable epilepsy and its associations to various seizure characteristics, such as seizure localization and years with diagnosis.

Memory

Memory is a complicated process encompassing various brain regions and pathways and has been defined as the capacity to retain information and utilize it for adaptive purposes (Fuster, 1997).Even though this definition is commonly cited, memory is now thought to be much more nuanced. Memory is usually divided into two broad categories, short term memory and long-term memory (Fuster, 1997; Lezak, 2012). Short term memory can be further broken down into two parts: sensory memory and working memory . Sensory memory refers to the ability to retain sensory information (taste, touch, sight, hearing, smell) and occurs within milliseconds of the stimuli (Lezak, 2012). Working memory has been defined as the ability to hold information in mind, manipulate it, and then recite that

information (Lezak, 2012). For information to be successfully stored in long-term memory, it must first be encoded, which requires intact short-term memory. Long term memory can also be broken down into two separate parts: explicit and implicit memory. Explicit, or declarative, memory is the learning and long-term memory of events and facts and is considered available to consciousness (Binder et al., 2009). Implicit, or non-declarative, memory, on the other hand, is considered "nonconscious" (Lezak, 2012). Implicit memory also includes procedural memory, tasks or skills that don't require conscious thought to retrieve, such as riding a bicycle (Lezak, 2012). These memory systems can operate independent of one another. For example, patient HM, who became famous for his bilateral hippocampal resection that prompted better understanding of memory, lacked the ability to encode new information. However, he learned to play the piano after daily practice, even though he didn't remember learning this skill (Lezak, 2012).

Encoding and retrieval are two separate and critical processes in memory. Encoding refers to the process where information successfully enters the memory system for storage while retrieval refers to spontaneously recalling stored information (Lezak, 2012). Memory difficulties can occur anywhere in the encoding, retrieval, or storage processes. Understanding where the breakdown occurs can be informative regarding localized or regional brain dysfunction. Encoding refers to the process where information successfully enters the memory system for storage while retrieval refers to spontaneously recalling stored information (Lezak, 2012). Often "memory problems" are lumped together without specifying which portion of the process is being affected. For example, individuals with anterograde amnesia have a problem with encoding, in which new information is not entered into the memory system (Lezak, 2012). Individuals with retrieval problems can make and

store memories and information properly, but have trouble accessing it (Lezak, 2012). An example of this is the tip-of-the-tongue phenomenon, where an individual can't recall a familiar word but can recall similar words (Brown & McNeill, 1966).

Declarative memory also has two subtypes: episodic and semantic. Episodic refers to 'events' while semantic refers to 'facts.' Additionally, verbal, and visuospatial memory systems comprise different pathways within the brain. Verbal memory falls under the umbrella of declarative memory, is considered a form of semantic memory, and is typically associated with the left hemisphere of the brain. Visuospatial memory pathways are typically associated with the right hemisphere of the brain (Ungerleider et al., 1998). Generally, verbal memory functioning is assessed with list-learning tasks and story recall tasks. The current study focuses on list learning tasks. Focusing on list-learning allows for comparison between standardized and experimental tasks, both of which will be discussed later in the proposal. Additionally, electroencephalogram (EEG) data was recorded during the experimental list-learning tasks allowing for analysis of EEG data and memory formation.

There are multiple indices used to examine various aspects of verbal memory performance. Clinically, the most common index of immediate verbal learning is total words recalled across multiple learning trials, which represents the number of words on the list the participant was able to successfully remember over multiple exposures to the stimuli. Spontaneous recall, although similar, measures how many words were recalled without the provision of cues after a brief distraction. Delayed recall, another major clinically relevant index, measures how many words were remembered after a delay or break, often approximately twenty minutes have elapsed, and other tasks completed in the interim. Cued recall measures the number of words remembered with the assistance of a verbal, typically

semantic, cue. Cues vary from task to task. For example, in most list learning tasks, the cue is a common category for a subset of the words on the list, e.g., clothing, tools, fruits, etc. Whereas with story recall tasks, the cue is a small detail about the story.

Hippocampus

The brain region most often considered in learning and memory is the hippocampus (Dhikav & Anand, 2012). The hippocampus is a small seahorse shaped structure located deep within the bilateral medial temporal lobes of the brain (Patel et al., 2020). The temporal lobes' primary functions are speech perception, hearing, and episodic memory, and these lobes assist with phonological, semantic, social, and visual functions (Patel et al., 2020). The primary function of the hippocampus is considered to be the process for long-term memory storage. The famous patient, H.M., who had bilateral temporal lobe resection surgery (including both hippocampi) was unable to encode new episodic memory. The hippocampus plays an important role in the formation and consolidation of memories as well as in the process of memory retrieval (Dhikav & Anand, 2012; Jin & Maren, 2015). Reduction in hippocampal volume has been associated with declines in memory performance (Pohlack et al., 2014). Hippocampal volume ratio is the ratio of the size of the hippocampus to the rest of the brain, often referred to as hippocampal volume. The hippocampus is approximately 100 times smaller than the cortex with the hippocampus being roughly 3-3.5 cm, and the rest of the cortex 320-420 cm (Gilbert & Brushfield, 2009). Hippocampal atrophy, i.e., hippocampi are smaller than expected, is seen in a variety of disorders from Alzheimer's dementia to depression and bipolar disorder. The hippocampus is one of the few brain structures where neurogenesis continues during adult life, meaning that atrophy may not be permanent (Dhikav & Anand, 2012). Nonetheless, hippocampal atrophy is often associated with memory deficits (Ferrarini et al., 2014).

Neuropsychology

Even with continued advances in neuroimaging, the gold standard for measuring the function of these brain regions affected by a disorder is neuropsychological assessment. The APA defines neuropsychology as a specialty field within clinical psychology that focuses on understanding the relationship between brain and behavior, particularly as these relationships can be applied to the diagnosis of brain disorder, assessment of cognitive and behavioral functioning, and the design of effective treatment (*Clinical Neuropsychology*, n.d.). This field uses standardized tests, normed on samples representative of the population, to assess cognitive and behavioral functioning. These measures can highlight an individual's cognitive strengths and deficits, and the resulting cognitive profile can assist with the diagnosing of psychological and physiological disorders.

A commonly used standardized neuropsychological test to measure learning and memory of unstructured verbal information is the California Verbal Learning Test – 2nd Edition (CVLT-II). This measure is used to assess verbal memory abilities in adults and older adolescents. The test is formatted as a list learning task, with 16 words presented verbally over multiple trials. The participant is asked to recall the words presented multiple times throughout the test, allowing for a nuanced understanding of the individual's immediate learning process. Another measure used to understand verbal memory performance is the Rey Auditory Verbal Learning test or RAVLT. Like CVLT-II, RAVLT is a list learning task where participants are presented a 15-item word list. The participants are asked to recall the words presented after each administration and again after a time delay.

While CVLT-II and RAVLT are commonly used list learning tasks to measure verbal memory performance, there are other verbal memory measures that are also used. The

Hopkins Verbal Learning Test – Revised (HVLT-R) is a list learning task with 12 nouns presented over three trials. Clinically, this test is mostly used with older adults, however the test is normed for ages 16 and older. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) includes a verbal list learning task of 10 words and a verbal story component. The RBANS is often used on older adults, with inpatient populations, or as a screening tool for major neuropsychological deficits. The RBANS was developed to be repeated, as the title implies, and has four versions, allowing for comparisons over time. Though these measures have proven to be reliable and valid measures of assessing verbal memory, there has yet to be a measure that can be repeated on a frequent or daily basis. CVLT-II has shown to have test-retest reliability after a year (Alioto et al., 2017). Though some studies suggest that CVLT-II can be administered after 30 days (Woods et al., 2006). While the RBANS has been shown to be reliable with shorter intervals of time (Wilk et al., 2002), the test is limited to four versions.

Study Purpose

Over time, there has been better understanding of epilepsy and the physical and cognitive symptoms, especially learning and memory, associated with the disorder. However, additional understanding of the mechanisms effecting the cognitive changes is needed. Memory tests that can be re-administered frequently are needed. This can assist in understanding the progression of cognitive changes and management of the disorder, hopefully leading to an improvement in quality of life. This proposal investigates how different epileptic demographics relate to memory performance, as well as the relationship between hippocampal volume, memory performance and these different demographic factors, such as seizure location, age of onset and handedness.

Aims

The primary goal of this study is to investigate aspects of verbal memory performance in relation to hippocampal volume ratio and seizure characteristics like seizure localization, seizure onset, and other demographic factors. Additionally, we will investigate the psychometric properties of an experimental memory task that can be administered daily to patients with intractable epilepsy and potentially other memory disorders.

Specifically, the aims of the study are to:

1. Compare the experimental verbal memory task to standardized memory measures in patients with intractable epilepsy.
    a. Hypothesis 1. I hypothesize that participants with intractable epilepsy will perform similarly on both the standardized and experimental verbal memory measures on some of the indices, specifically, spontaneous recall. However, I will explore other memory indices in the comparison of the experimental and standardized tasks allowing for additional understanding of memory function.
2. Examine relationships between hippocampal volume ratio, seizure localization, and memory performance as measured by both the experimental and standardized verbal learning and memory tasks in adults with intractable epilepsy.
    a. Hypothesis 2a: I hypothesize that memory indices as measured by both the experimental and standardized tests are negatively associated with hippocampal volume ratio.
    b. Hypothesis 2b. I hypothesize that seizure localization in the temporal lobe or hippocampus will be significantly associated with memory performance on both the experimental and standardized memory tests.

3. Examine the relationships among hippocampal volume ratio and memory performance as measured by both the experimental and standardized tests, and demographic factors, i.e., . age of seizure onset, length of epilepsy diagnosis, handedness, and bilingual status.
    a. Hypothesis 3. I hypothesize that the relationship between hippocampal volume and memory performance, measured by both the experimental and standardized tests, will be mediated by age of seizure onset, length of epilepsy diagnosis, handedness, and bilingual status .

Methods

Participants and Setting

Patients diagnosed with intractable epilepsy from the University of Texas (UT) Southwestern and Parkland hospitals were recruited to take part in this study with the Texas Computational Memory lab (Bradley Lega, MD; Principal Investigator). All participants were patients with intractable epilepsy who underwent neurosurgery. Participants had stereo electroencephalogram (sEEG) electrodes implanted into various areas of their brain as part of their treatment plan and to assist in determining seizure localization. Patients stayed in the Epilepsy Monitoring Unit (EMU) of UT Southwestern or Parkland. Participation in the experimental tasks occurred only during their stay at the EMU while electrodes were implanted.

Clinical Procedure

Medication adjustments were attempted to control seizure frequency. If multiple medication adjustments proved unsuccessful in controlling the patient's seizures, the patient was considered for surgery. Patients completed a comprehensive neuropsychological assessment to assist in identifying seizure localization and cognitive functioning. The assessment also assisted in EEG electrode placement. Patients then underwent depth electrode implantation surgery and stayed in the EMU for observation and assessment to localize their seizures. Depending on the location and type of seizures, patients were considered for resection surgery or surgical implant in controlling their seizures.

Measures

Participants completed a series of both experimental and standardized memory tasks during their stay in the EMU and prior to patients' undergoing surgery. The experimental tasks were administered up to two times a day, depending on participant willingness and

seizure activity. Experimental memory tasks included a verbal list learning memory task, a paired associates memory task, and spatial navigation memory tasks. This study focuses on the verbal list learning task.

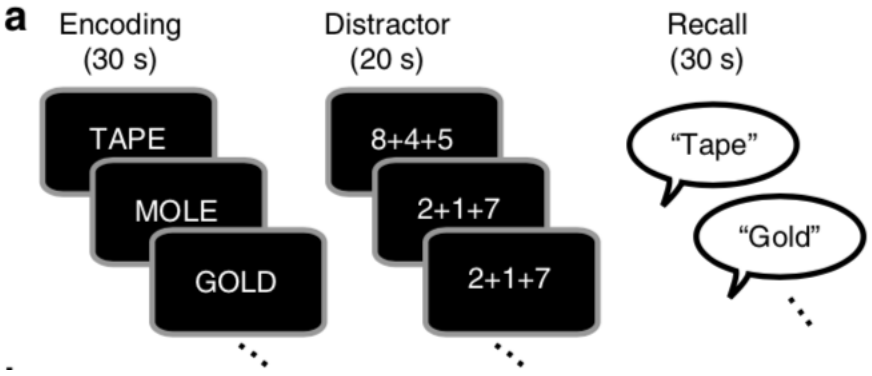
Additionally, patients were administered a comprehensive neuropsychological battery for clinical purposes. This neuropsychological battery was used as a baseline for their cognitive functioning, to identify strengths and weaknesses, and to assists in their clinical treatment. Follow-up neuropsychological batteries are given depending on clinical need. The battery included a test of general cognitive functioning, IQ, either the Weschler's Adult Intelligence Scale (WAIS) (*Wechsler Adult Intelligence Scale | Fourth Edition*, n.d.); or the Weschler's Abbreviated Scale of Intelligence) (WASI) (*WASI-II Wechsler Abbreviated Scale Intelligence | 2 Ed*, n.d.); Brief Visuospatial Memory Test Revised (BVMT-R) (*Brief Visuospatial Memory Test-Revised | BVMT-R*, n.d.), Rey Complex Figure (*Rey Complex Figure Test and Recognition Trial | RCFT*, n.d.), Weschler's Logical Memory (WMS) (*WMS-IV Wechsler Memory Scale 4th Edition*, n.d.), a verbal memory task (California Verbal Learning Test II or Rey Auditory Verbal Learning Test) (*California Verbal Learning Test | Third Edition*, n.d.; "Rey Auditory Verbal Learning Test (RAVLT)," n.d.); and other measures depending on clinical need.

Experimental Memory Task

The experimental memory task is a list-learning task and was administered multiple times throughout participants' stay and consisted of multiple trials. Each trial consisted of encoding a list of words, a math distractor, and free recall sections. During the encoding section, participants were shown a list of twelve words, one at a time for a duration of 30 seconds, on a computer screen. These words were randomly generated by the computer from

a larger master list. Following the encoding section, a math distractor task was administered, where participants completed simple addition problems for 30 seconds. The number of problems completed varied based on how quickly the participants completed the problems. Following the distractor, the participants were asked to orally recall as many words from the word list and were given 30 seconds to remember as many words as they could. This process was repeated multiple times in one session. Each list of words presented differed from the previous list. The computer program randomly selected words from a master list to provide different words for each trial without repeating previous words. There are a total of 12 or 25 trials in each testing session depending on whether the participant completed the short form or long form of the task. Participants completed multiple sessions throughout their stay in the EMU with the number of sessions differing based on the length of the patient's clinical stay in the EMU. All participation in the experimental tasks were voluntary and participants could stop at any time.

Figure 1. Experimental Free Recall Task



California Verbal Learning Test – II (CVLT-II)

The CVLT-II is a verbal list-learning task consisting of a verbal presentation by the examiner of 16 words from 4 different categories (animals, vegetables, furniture, and modes of transportation). They list was presented five times. Following the fifth trial, participants are presented with a new list of 16 words and asked to recall as many as they can. They are then asked to recall as many words as they can from the first list that was presented to them five times. This is followed by a 20-minute break during which they complete different neuropsychological tasks. After about 20-minutes, they are asked to recall as many words as they can from the first list without a stimulus or cue. They are then given four cues (animals, vegetables, furniture, and modes of transportation) and asked to recall words from the list that belong in that category. A recognition section follows, where words are presented one at a time and participants must answer if the word was in the first list.

Rey Auditory Verbal Test (RAVLT)

The RAVLT is also a verbal list-learning task similar to the CVLT-II for which the participant is orally presented with 15 words and the list is repeated over five trials. The participants are then presented with a second list of 15 words. They are then asked to recall the words from the original list that was presented multiple times. There is a 30-minute delay, then the participants are asked to recall the list of words that was presented multiple times.

Weschler Adult Intelligence Scale (WAIS-IV) – Similarities Subtest

The Similarities subtest of the WAIS is a verbal abstract reasoning test. The subtest consists of 18 pairs of words. The participant is asked to verbally identify the similarity between the two words. For example, “how are dog and cat alike?” The test ends after

completing all 18 pairs of words or after three incorrect responses in a row. The test measures verbal reasoning, abstract thinking skills and concept formation skills.

Weschler's Memory Scale (WMS) – Logical Memory Subtest

The Logical memory subtest of the WMS is a verbal memory measure. The subtest consists of two stories presented orally one at a time. Participants are asked to recall as much of the story as they can. After a delay of around 25 minutes, participants are asked to recall the two stories one at a time. The subtest ends with a recognition section where participants are asked yes or no questions about the stories.

Analyses

The data have been cleaned and examined for entry error by the Texas Computational Memory Lab. Hippocampal volume data was compiled by clinical data specialists at the Texas Computational Memory Lab. Descriptive statistics were conducted for all variables of interest for normality and outliers.

AIM 1. To complete the analysis for Aim 1, correlational analyses will be used to investigate the verbal learning and memory performance on the experimental task and the standardized tests including various indices.

AIM 2. To complete the analyses for Aim 2, separate analyses will be performed for the relationships between hippocampal volume ratio and memory performance and seizure location and memory performance. Correlational analysis will be used to investigate hippocampal volume ratio and memory performance. Analysis of variance will be used to compare verbal memory performance and seizure localization.

AIM 3. To complete the analysis for the final aim, regression analysis will be used to investigate hippocampal volume ratio and memory performance using the demographic

factors as moderating variables. Demographic factors such as years with seizures, handedness, and bilingual status will be considered.

Results

Demographics

Patient demographics are presented in Table 1 delineated by sex. Independent-sampled T-tests were completed to compare the male and female demographics for age, age of seizure onset, duration of years with epilepsy, and hippocampal volume. Pearson's chi-squared tests were completed to compare male and female demographics for race, ethnicity, handedness, language dominance, hemisphere of onset, and seizure onset zone. Majority experienced seizure onset in the temporal lobe, 63.4% for females and 49.0% for males. This difference was statistically significant (p=0.036). Language dominance, though undetermined for most cases, tended toward the left hemisphere in both men (27.8%) and women (39.6%). This difference was approaching significance, though not statistically significant (p=0.084). Left hippocampal volume ratio, though only available for a small subset of individuals (n=17), was 0.61 cm^3 on average for women and 0.62 cm^3 on average for men. Right hippocampal volume ratio was 0.63 cm^3 on average for women and 1.33 cm^3 on average for men. Right hippocampal volume ratio was significantly different for males and females (p=0.002).

Table 1. Demographic Variables

		Female N=91	Male N=97	*P-value*
Age, years	mean	38.0	37.0	*0.414*
Age of onset, years	mean	22.6	19.8	*0.488*
Age of onset, categories	0-10 years	16.0 (20.0%)	20.0 (24.1%)	
	11-20 years	21.0 (26.3%)	28.0 (33.7%)	
	21-30 years	20.0 (25.0%)	18.0 (21.7%)	
	30+ years	23.0 (28.8%)	17.0 (20.5%)	

Duration with Epilepsy, years	Mean	15.87	17.98	*0.610*
Race	Caucasian	69.0 (75.8%)	82.0 (84.5%)	*0.327*
	African American	11.0 (12.1%)	4.0 (4.1%)	*0.327*
	Asian	1.0 (1.1%)	2.0 (2.1%)	*0.327*
	American Indian/Alaska Native	2.0 (2.2%)	1.0 (1.0%)	*0.327*
	Other	1.0 (1.1%)	2.0 (2.1%)	*0.327*
	Unknown	7.0 (7.7%)	5.0 (5.2%)	*0.327*
Ethnicity	Hispanic	13.0 (14.3%)	12.0 (12.4%)	*0.739*
	Non-Hispanic	73.0 (80.2%)	79.0 (81.4%)	*0.739*
	Unknown	5.0 (5.5%)	5.0 (5.2%)	*0.739*
Handedness	Right	68.0 (74.7%)	60.0 (61.9%)	*0.508*
	Left	12.0 (13.2%)	12.0 (12.4%)	*0.508*
	Ambidextrous	0.0 (0.0%)	3.0 (3.1%)	*0.508*
Language Dominance	Right	2.0 (2.2%)	0.0 (0.0%)	*0.084*
	Left	36.0 (39.6%)	27.0 (27.8%)	*0.084*
	Bilateral	1.0 (1.1%)	4.0 (4.1%)	*0.084*
	Bilateral, right	4.0 (4.4%)	0.0 (0.0%)	*0.084*
	Bilateral, left	7.0 (7.7%)	12.0 (12.3%)	*0.084*
	Undetermined	41.0 (45.1%)	54.0 (55.7%)	*0.084*
Hemisphere of Seizure Onset	Right	21.0 (23.1%)	34.0 (35.1%)	*0.318*
	Left	41.0 (45.1%)	34.0 (35.1%)	*0.318*

	Bilateral	18.0 (19.8%)	17.0 (17.5%)	*0.318*
	Undetermined	11.0 (12.1%)	12.0 (12.4%)	*0.318*
Seizure Onset Zone	Temporal Lobe	59.0 (63.4%)	48.0 (49.0%)	*0.036**
	Other	19.0 (20.4%)	32.0 (32.7%)	*0.036**
Left Hippocampal Volume Ratio	Mean (cm^3)	0.61	0.62	*0.907*
Right Hippocampal Volume Ratio	Mean (cm^3)	0.63	1.33	*0.002***

*$p<0.05$, **$p<0.01$

Measures

The neuropsychological tests are presented in Table two delineated by sex. Two-tailed t-tests were completed comparing test performance for male and female participants. P-values were calculated using a two-sampled t-test where equal variance is not assumed.

Table 2. Test scores by sex (mean and standard deviation)

	Female N=91	Male N=97	*P-value*
RAVLT			
Total Learned, Words	48.0 (9.0)	44.0 (10.0)	*0.056*
Short Delay, Words	9.0 (3.0)	7.0 (3.0)	*0.015**
Long Delay, Words	9.0 (4.0)	7.0 (3.0)	*0.024**
CVLT-II			
Total Learned, Words	44.0 (11.0)	44 (10.0)	*0.997*

Short Delay Free Recall, Words	13.0 (16.0)	9.0 (3.0)	*0.382*
Long Delay Free Recall, Words	8.0 (4.0)	9.0 (3.0)	*0.831*
Long Delay Cued Recall, Words	8.3 (4.3)	9.1 (3.3)	*0.602*
Standardized (CVLT and RAVLT) Combined			
Trial 1, percent	0.41 (0.12)	0.37 (0.11)	*0.045**
Total Recalled, percent	0.62 (0.14)	0.58 (0.13)	*0.070*
Experimental Task, Session 1			
Total, Percent Recalled	0.25 (0.12)	0.23 (0.11)	*0.228*
Trial 1, Percent Recalled	0.28 (0.20)	0.26 (0.21)	*0.313*
Trial 2, Percent Recalled	0.29 (0.19)	0.25 (0.18)	*0.073*
Trial 3, Percent Recalled	0.29 (0.22)	0.27 (0.19)	*0.289*
Trial 4, Percent Recalled	0.29 (0.21)	0.24 (0.17)	*0.095*
WMS			
Logical Memory I, scaled score	9.0 (3.0)	9.0 (4.0)	*0.481*
Logical Memory II, scaled score	9.0 (4.0)	8.0 (4.0)	*0.314*
COWA			
FAS, Words	29.0 (11.0)	29.0 (12.0)	*0.941*
Animals, Words	16.0 (6.0)	17.0 (5.0)	*0.575*
WAIS			
Coding, scaled score	8.0 (3.0)	8.0 (3.0)	*0.546*
Symbol Search, scaled score	6.0 (3.0)	5.0 (2.0)	*0.292*
FSIQ, Standard Score	85.0 (14.0)	92.0 (14.0)	*0.009***
GAI, Standard Score	88.0 (15.0)	95.0 (14.0)	*0.010**
Trails A, seconds	35.5 (18.0)	35.4 (28.5)	*0.981*

RAVLT – Rey Auditory Verbal Learning Test, CVLT – California Verbal Learning Test, Standardized Combined is a composite variable containing RAVLT and CVLT scores, Experimental Task is the experimental list learning task, WMS – Weschler Memory Scale, COWA – controlled oral word association test, WAIS – Weschler Adult Intelligence Scale, *p<0.05, **p<0.00

Performance on the Full-Scale Intelligence Quotient (FSIQ) and General Ability Index (GAI) were significantly different for male and female participants. Similarly, the RAVLT short delay and long delay showed differences between male and female participants. No other standardized measures had significant between group differences. The experimental memory task showed no significant difference between male and female participants.

A combined variable was created by combining CVLT and RAVLT verbal memory measures. Participants were given either CVLT or RAVLT. Descriptive statistics of CVLT and RAVLT were calculated to ensure the measures were similar in mean and standard deviation. Two combined variables were calculated. The first variable contained percentage correct in the first trial of either CVLT or RAVLT, named hereafter as Standard Combined List 1. The second variable contained total percentage correct during all five trials of CVLT or RAVLT, named hereafter as Standard Combined Total. Performance on the Standardized Combined List 1 was significantly different for males and females ($p<0.05$).

Aim 1

Correlations

Bivariate correlations were run to assess the relationship between memory performance measures (list 1 score and total word score where appropriate): RAVLT, CVLT, WMS Logical Memory, and the Experimental task. Table 3 shows correlation data for these measures. RAVLT, list 1 was significantly correlated to RAVLT, total words recalled ($r = .781$, $p < 0.01$), WMS LM I ($r = .397$, $p < 0.01$) and II ($r = .463$, $p < 0.01$), and the Experimental task session 1, list 1 ($r = .537$, $p < 0.01$). Experimental task total words recalled

was significantly correlated to the experimental task, session 1, list 1 (r = .550, $p < 0.01$), but no other standardized measures listed in Table 3.1. Experimental Task, Session 1, List 1, was significantly correlated with RAVLT, list 1 (r = .537, $p < 0.01$) and RAVLT, total words (r = .496, $p < 0.01$).

Table 3. Pearson Correlations for Memory Indices

Measure	1	2	3	4	5	6	7	8
1. RAVLT, List 1	-							
2. RAVLT, Total Words	.781**	-						
3. CVLT, List 1	b	b	-					
4. CVLT, Total Words	b	b	.715**	-				
5. WMS LMI	.397**	.471**	.481*	.585**	-			
6. WMS LMII	.463**	.497**	.390	.445*	.902**	-		
7. Experimental, Session 1, List 1	.537**	.496**	.250	.345	.282	.315	-	
8. Experimental, Session 1, Total recalled	.285	.339	.074	.446	.277	.300	.550**	-

*$p<0.05$, **$p<0.01$, b no participants with both tasks

Bivariate correlations were run to assess the relationship between the combined standardized variables, other verbal measures, and the experimental task. Table 4 shows correlation data for these measures. Standardized list 1 was significantly correlated to standardized total recalled, WMS LM I, WMS LM II, COWA FAS, COWA Animals, BNT and the experimental task session 1 list 1. Standardized total recalled was significantly correlated with WMS LM I, WMS LM II, COWA FAS, COWA Animals, BNT, the experimental task session 1 list 1, and experimental task session 1 total recalled.

Additionally, the experimental task session 1 total recalled was significantly correlated with COWA FAS and Animals.

Table 4. Pearson Correlations for Verbal Measures

Measure	1	2	3	4	5	6	7	8	9
1.Standardized , List 1	-								
2. Standardized, Total recalled	0.782**	-							
3. WMS LM1	0.410**	0.473**	-						
4. WMS LMII	0.455**	0.483**	0.901**	-					
5. COWA FAS	0.239*	0.365**	0.069	0.107	-				
6. COWA Animals	0.355**	0.467**	0.371**	0.418**	0.542**	-			
7. BNT	0.307**	0.385**	0.279**	0.263**	0.418**	0.371**	-		
8. FR, Session 1, List 1	0.357*	0.383**	0.282	0.315	0.262	0.104	-0.001	-	
9. FR, Session 1, Total recalled	0.216	0.348*	0.277	0.300	0.342*	0.362*	0.194	0.550*	-

*$p<0.05$, **$p<0.01$

To assess the relationship between processing speed, IQ measures, and verbal memory, bivariate correlations were run. Trails A was significantly correlated with standardized total recalled, WAIS Coding, WAIS FSIQ, and WAIS GAI. Standardized list 1 was significantly correlated with WAIS coding. Standardized total was significantly correlated to WAIS coding and WAIS FSIQ. Both experimental task session 1 list 1 and session 1 total were significantly correlated to WAIS coding.

Table 5. Pearson Correlations for processing speed and intelligence measures

Measure	1	2	3	4	5	6	7	8	9
1.Standardized , List 1	-								
2. Standardized, Total recalled	0.782**	-							
3. Trails A	-0.101	-0.217*	-						
4. WAIS Coding	0.311**	0.361**	-0.543**	-					
5. WAIS SS	-0.208	0.202	-0.551	0.771**	-				
6. WAIS FSIQ	0.174	0.255**	-0.344**	0.229*	0.666*	-			
7. WAIS GAI	0.146	0.176	-0.337**	0.215*	0.682	0.995**	-		
8. FR, Session 1, List 1	0.357*	0.383**	-0.207	0.339*	0.786	0.188	-0.109	-	
9. FR, Session 1, Total recalled	0.216	0.348*	-0.283	0.382*	0.813	0.228	0.149	0.550**	-

*p<0.05, **p<0.01

Bivariate correlations were run to assess the relationship between the standardized measures and the experimental task. Standard Combined List 1 was significantly correlated with Standard Combined Total. Experimental Session 1 Total was positively correlated with Standard Combined Total. The first list of Experimental Session 1 was significantly correlated with Standard combined list 1, Standard combined total, and Experimental Session 1 total. Experimental list 2 and list 3 were also positively correlated with Standard Combined Total.

Table 6. Pearson Correlations for Standardized Combined Task and the Experimental Task, Session 1

Measure	1	2	3	4	5	6	7
1. Standardized Combined, List 1	-						
2. Standardized Combined, Total	0.782**	-					
3. Experimental, Session 1, Total	0.216	0.348*	-				
4. Experimental, Session 1, List 1	0.357*	0.383**	0.550**	-			
5. Experimental, Session 1, List 2	0.179	0.359*	0.545**	0.264*	-		
6. Experimental, Session 1, List 3	0.240	0.438**	0.552**	0.311**	0.702**	-	
7. Experimental, Session 1, List 4	0.319	0.281	0.591**	0.457**	0.484**	0.513**	-

*p<0.05, **p<0.01

Table 7. Pearson Correlations for Standardized Combined Task and Experimental Task, Session 2

Measure	1	2	3	4	5	6	7
1. Standardized Combined, List 1	-						
2. Standardized Combined, Total	0.782**	-					
3. Experimental, Session 2, Total	-0.228	0.127	-				
4. Experimental, Session 2, List 1	-0.384	0.065	0.462**	-			
5. Experimental, Session 2, List 2	-0.317	0.207	0.528**	0.024	-		
6. Experimental, Session 2, List 3	0.242	0.522	0.604**	0.281	0.326*	-	
7. Experimental, Session 2, List 4	-0.081	-.006	0.643**	0.171	0.369*	0.673**	-

*p<0.05, **p<0.01

Aim 2

Bivariate Pearson correlations were run to test the association between hippocampal volume ratio and memory performance. Hippocampal volume ratio was not significantly associated with memory performance on the standardized or experimental memory tasks.

Table 8. Pearson correlations for Standardized Combined Task and Hippocampal Volume Ratio

Measure	1	2	3	4
1. Standardized Combined, List 1	-			
2. Standardized Combined, Total	0.782**	-		
3. Hippocampal Volume Ratio Left	-0.977	0.244	-	
4. Hippocampal Volume Ratio Right	-0.931	0.114	0.180	-

*p<0.05, **p<0.01

Table 9. Pearson Correlations for Experimental Task and Hippocampal Volume Ratio

Measure	1	2	3	4	5	6	7
1. Hippocampal Volume Ratio Left	-						
2. Hippocampal Volume Ratio Right	0.180	-					
3. Experimental, Session 1, Total	-0.172	0.010	-				
4. Experimental, Session 1, List 1	0.079	-0.089	0.383**	-			
5. Experiemtnal, Session 1, List 2	0.276	-0.065	0.359*	0.179	-		
6. Experimental, Session 1, List 3	-0.312	-0.167	0.438**	0.240	0.552*	-	
7. Experimental, Session 1, List 4	0.282	-0.206	0.339*	0.347*	0.451*	0.257**	-

*p<0.05, **p<0.01

A one-way ANOVA was completed to comparing seizure onset in the temporal lobe to other brain regions and memory performance on both the standardized and experimental memory measures. There was not a significant between group difference for the experimental or the standardized memory tasks.

Table 10. ANOVA Seizure Onset Zone (Temporal Lobe vs Other Brain Region)

Measure	Temporal Lobe		Other		*F*(,)	η^2
	M	*SD*	*M*	*SD*		
Standardized Combined						
Trial 1	0.39	0.11	0.42	0.10	0.975	0.011
Total	0.61	0.13	0.63	0.13	0.921	0.340
Experimental Session 1						
List 1	0.26	0.20	0.28	0.22	0.215	0.010
List 2	0.27	0.19	0.26	0.18	0.132	0.005
List 3	0.30	0.21	0.24	0.21	1.143	0.054
List 4	0.27	0.19	0.25	0.20	0.169	0.006
Total	0.24	0.11	0.23	0.11	0,042	0.000

Aim 3

Prior to running the regression models, the variables were centered creating a mean of zero for the variables and the model, allowing for easier interpretation of the results. A regression was completed with standardized total performance as the dependent variable and

hippocampal volume ratio as the independent variable. Age of onset was included as a moderating variable. No significant relationship was found.

Additional regression analyses were run with the experimental memory task as a dependent variable and the standardized memory performance as an independent variable. The model was significant as well as the coefficient. When additional modifier variables (like age of seizure onset, handedness, language dominance) were added to the model, the model and coefficients were no longer significant. Additionally, when other neuropsychological measures were added to the model, the regression was no longer significant.

Table 11. Regression Analysis Standardized Measures and Experimental Measure

Effect	Estimate	*SE*	95% CI		*p*
			LL	*UL*	
Fixed effects					
Intercept	0.020	.018			.265
Standardized Total	0.324	0.131	0.348	0.348	0.018

Discussion

This study investigated verbal memory performance and hippocampal volume ratio in adults with intractable epilepsy. A series of bivariate Pearson correlations, ANOVAs and linear regressions were completed to investigate the three specific aims. The standardized memory tasks and the experimental memory task were significantly correlated. The experimental task was also correlated to other neuropsychological measures. Hippocampal volume ratio was not significantly correlated to memory performance nor was seizure onset zone. Regression analyses showed no significant relationship between hippocampal volume ratio, verbal memory performance, and demographic factors. Regression analysis of the experimental and standardized verbal list learning tasks was statistically significant. The set of analyses sought to better understand the relationship between memory performance, various demographic factors, and hippocampal volume in individuals with intractable epilepsy. These findings suggest that the experimental memory task is a promising measure for repeatable memory assessment. Additionally, these findings suggest that seizure demographics, when examined at this level, are not associated with memory performance, specifically spontaneous recall.

Aim 1

Aim 1 sough to compare the experimental verbal memory task to standardized memory measures in patients with intractable epilepsy. I hypothesized that the standardized memory tasks and experimental memory task would be similar on spontaneous recall. Correlational and regression analyses were completed and indicated that a significant association was present, supporting this hypothesis.

Though additional analyses are needed to further the understanding of the experimental task, potential implications appear promising. The majority of

neuropsychological tests cannot be regularly administered due to practice effects and limited number of alternative forms. Majority of tasks, even if delivered on a digital interface, are still administered by a psychometrist. A task that can be administered with such frequency and yield consistent results could make serial testing possible. This would be particularly helpful in situations where rapid change occurs, or regular monitoring of symptoms is needed. Clinically, this type of testing could lead to better understanding of cognitive symptoms over time.

Poor performance on memory measures is often considered an indicator of seizure activity in neuropsychological testing. Often, performance on verbal and visuospatial memory tasks are used to help identify potential seizure localization. Though, it is argued that this is a simplistic view of hippocampal and memory involvement in epilepsy (Saling, 2009). The use of a repeatable verbal memory measure in individuals with epilepsy, could allow for understanding of any fluctuations in memory as well as differences pre- and post-seizure activity. Additionally, memory performance on neuropsychological measures does not correlate strongly to subjective memory complaints for these individuals (Reed, 2019). There is a need to better understand the nuances of cognitive difficulties and their subjective experience, which could inform how quality of life can be improved for people living with epilepsy.

Aim 2

Aim 2 sought to examine relationships between hippocampal volume ratio, seizure localization, and memory performance as measured by both the experimental and standardized verbal learning and memory tasks in adults with intractable epilepsy. I hypothesized that hippocampal volume ratio would be associated with memory performance

in this sample and that seizures that onset in the temporal lobe would be associated with worse memory performance outcomes. These hypotheses were not supported by the analyses done here. There are likely several possible reasons for this lack of findings. First, the sample size used to compare hippocampal volume to memory performance was quite small due to limited neuroanatomical data available. Additionally, the sample may be homogenous, potentially limiting noticeable differences. The analysis of seizure onset zones may be better studied by comparing all regions rather than just the temporal lobe to other brain regions. Comparing both brain regions and hemisphere of seizure onset may provide a more nuanced understanding of memory performance and seizure onset zones. Temporal lobe epilepsy is the most common type of epilepsy, meaning there may have been to many participants with temporal lobe involvement as compared to other brain regions. Additionally, in more recent studies, individuals with temporal lobe epilepsy had decreased neural connectivity (Fleury et al., 2022), suggesting that assessing connectivity may provide a better understanding of temporal lobe epilepsy and memory.

Aim 3

Aim 3 sought to examine the relationships among hippocampal volume ratio and memory performance as measured by both the experimental and standardized tests, and demographic factors. I hypothesized that the relationship between hippocampal volume and memory performance would be mediated by age of seizure onset, length of epilepsy diagnosis, handedness, and bilingual status. Due to limited neuroanatomical data, the results should not be interpreted. Nonetheless, the results were not significant, and the hypothesis was not supported.

Hippocampal involvement in memory performance has been clear since the pivotal findings following patient H.M.'s bilateral hippocampal resection. In more recent years, there has been understanding that hippocampal atrophy can also lead to memory deficits in patients (Ferrarini et al., 2014). Reductions in hippocampal volume have been seen in a variety of disorders, including epilepsy, PTSD, and major depressive disorder (Anand & Dhikav, 2012). Though a significant relationship between hippocampal volume and memory performance was not supported in this study, continued understanding of these relationships are important. Additionally, continued understanding of how these relationships are moderated by seizure demographics, like age of onset, language dominance, and bilingual status, are increasingly important. It is also worth noting that hippocampal volume and hippocampal atrophy are two different variables. It is possible that the individuals in the study did not have hippocampal atrophy, because only one timepoint of hippocampal volume was available for analysis. Thus, a change in size due to atrophy could not be detected.

Limitations

There are a few limitations to consider. This was a secondary data analysis of a sample of a clinical population. Thus, measures were originally intended for clinical uses in the treatment of patients' epilepsy. Because neuropsychological measures were gathered for clinical purposes, tests varied across participants. Many of the indices that I wanted to analyze were unavailable in the neuropsychological data, such as primacy, and recency effects. Additionally, missing data created smaller than ideal sample sizes for robust analysis. SPSS was used for the analyses, and though it is a commonly used statistical software, other software packages are better equipped to deal with missing data points in analyses, such as M plus.

Future Directions

Even with various limitations, the analyses provided useful insights that may guide future analyses or studies. As additional data is collected, more robust analyses with larger sample sizes will be possible. Additionally, using a more sophisticated statistical software could allow for more options in dealing with missing datapoints.

There are specific analyses to consider for the future. For instance, when analyzing seizure onset zone, temporal lobe was compared to all other brain regions. An analysis comparing all brain regions or multiple brain regions could be done, including hemisphere of seizure onset. Additionally, when considering age of onset of epilepsy diagnosis, an analysis of years living with epilepsy or years with uncontrolled seizures, may provide more insight into seizures effects on memory performance.

Specific studies could be useful in further developing the experimental memory task. For instance, completing the task daily in a healthy or control sample could allow for a deeper understanding of the task's psychometric properties.

Conclusion

Epilepsy is a serious medical diagnosis that effects 1.2% of the United States population. Understanding memory in individuals with epilepsy and how seizure demographics and hippocampal volume affect these relationships will help further clinical treatment for these individuals. These analyses sought to understand how memory performance, hippocampal volume, and seizure demographics are associated.

I compared the experimental verbal memory task to standardized memory measures in patients using correlation analyses. My hypothesis that the tasks would be correlated was supported. I examined the relationships between hippocampal volume ratio, seizure localization, and memory performance as measured by both the experimental and standardized verbal learning and memory tasks. The hypothesis was not supported. Finally, I examine the relationships among hippocampal volume ratio and memory performance as measured by both the experimental and standardized tests, and demographic factors. The hypothesis was not supported in this sample.

By using bivariate correlations, ANOVA, and regression analyses, I was able to assess these relationships in this sample. I found that the experimental memory task and the standardized list learning memory tasks were significantly associated with one another. Additionally, hippocampal volume and was not associated with memory performance in this analysis and the relationships were not moderated by other demographic factors.

These findings provide useful insight in how to complete future analyses and further understanding of memory in this population. Additionally, the association between the experimental and standardized list learning measures are promising with the potential for development of additional repeatable memory measures.

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