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DEVELOPMENT OF A REPEATABLE OVERNIGHT MEMORY TASK TO STUDY THE EFFECT OF NOCTURNAL SEIZURES ON MEMORY

Nahal Destiny Heydari

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ST. JOHN'S UNIVERSITY
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by
Nahal Destiny Heydari

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Nahal Destiny Heydari

William Chaplin, PhD

ABSTRACT

DEVELOPMENT OF A REPEATABLE OVERNIGHT MEMORY TASK TO STUDY THE EFFECT OF NOCTURNAL SEIZURES ON MEMORY

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Memory impairment is a common comorbidity of epilepsy, particularly in patients with temporal lobe epilepsy (TLE) for whom the hippocampus and surrounding memory-dependent regions are directly involved in seizure activity. Sleep is known to facilitate memory consolidation processes; however, whether, or the extent to which, nocturnal seizures disrupt memory processes in TLE is unknown. Investigating the effect of nocturnal seizures on memory requires a task designed to assess memory in the morning for material learned the evening before a period of sleep, ideally over multiple days. Accordingly, we have created a psychometrically sound, word paired-associates (WPA) memory task with five alternate forms to assess overnight memory longitudinally. We selected comparable stimuli for the WPA task versions and piloted this task in a group of healthy controls. We subsequently began standardizing the task with healthy adults ages 18-55. We determined the feasibility and utility of the task procedure by administering the WPA task over three days to people with epilepsy admitted to an inpatient Epilepsy Monitoring Unit (EMU). Overall, we found that epilepsy patients performed poorer than healthy controls on the WPA task. We also examined the extent to which nocturnal seizures disrupted memory consolidation for these patients, and hypothesized that memory would be poorer in the morning following nights with nocturnal seizures

compared to nights without seizures in a within-subjects design. Although a small sample size precluded statistical analysis, data trended towards poorer memory performance after nights with nocturnal seizures. Further development and standardization of this task will result in a public domain, multi-form, computerized memory task that can be used in epilepsy and other neurological disorders to assess overnight memory at multiple time points for clinical and research purposes.

DEDICATION

To S.H.

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INTRODUCTION

The lifetime prevalence of epilepsy is 7.6 per 1000 individuals, currently affecting millions of people worldwide (Fiest et al., 2017). Epilepsy is accompanied by functional burdens beyond seizures, which can include debilitating and lifelong cognitive impairments that can compromise educational, social, and occupational achievement (Chin et al., 2011; Suurmeijer et al., 2001; Wo et al., 2017). Memory impairment is a common comorbidity of epilepsy, particularly in people with temporal lobe epilepsy (TLE), for whom the hippocampus is directly involved in seizure activity (Hermann et al., 1992; Lee et al., 2002). TLE is the most common form of focal epilepsy (Téllez-Zenteno & Hernández-Ronquillo, 2012), and verbal memory impairment has been well documented in patients with left temporal lobe seizures and left mesial temporal sclerosis (Saling et al., 1993; Saling, 2009; Mueller et al., 2012). Despite significant patient concern about memory difficulty, practitioners often fail to address memory problems, instead focusing primarily on seizure control (Fisher et al., 2000; McAuley et al., 2010). Given the prevalence of memory difficulty and its adverse impact on daily life, evaluating and managing memory problems warrants greater attention.

The etiology of memory impairment in epilepsy is likely multifactorial, including factors such as underlying neuropathology (Holmes, 2015), location and frequency of ictal and interictal discharges (Dodrill, 2004; Helmstaedter et al., 2003; Holmes, 2016), and adverse effects of anti-seizure medications (Hermann et al., 2010; Jokeit et al., 2005). Although it is well known that sleep plays a vital role in the consolidation of new memories, the impact of nocturnal seizures (i.e., seizures that occur during sleep) on these consolidation processes remains unclear.

The sleep-memory relationship has been well documented in healthy individuals (Diekelmann et al., 2009; Klinzing et al., 2019; Stickgold, 2005). Extensive research has shown that memories are not stored instantly, but undergo sleep-dependent consolidation processes (Drosopoulos et al., 2007; Marshall & Born, 2007; Stickgold, 2005). Consolidation processes provide a state in which new memories are transferred from the hippocampus to the neocortex for integration into long-term memories (Sutherland & McNaughton, 2000). Individuals with epilepsy most often experience difficulties with declarative memory, which involves the explicit recall of events and facts (Eichenbaum, 2000; Hermann & Seidenberg, 2008). Declarative memory relies primarily on temporal lobe processing, suggesting seizures arising from this area may disrupt consolidation processes and result in memory disturbances. Although it has been suggested that nocturnal seizures may disrupt memory consolidation (Bazil, 2002), the absence of properly designed studies to test this hypothesis leaves a significant gap in clinical knowledge.

The Relationship between Seizures and Sleep

In some patients, sleep reveals an active epileptic network that is not readily detectable during wakefulness (Halász et al., 2019). The occurrence of nocturnal seizures is highly variable, but has been shown to occur in up to 45% of people with epilepsy (Bazil & Walczak, 1997; Gibberd & Bateson, 1974; Goel et al., 2008; Janz, 1962; Kaleyias et al., 2011). Because they occur at night, nocturnal seizures are often unwitnessed, and patients frequently have no recall of these events, suggesting the prevalence of nocturnal seizures is likely underestimated, and their effects understudied (Bazil, 2004). Even when seizures occur outside of conscious awareness, there is strong

evidence that nocturnal seizures reduce sleep efficiency, as several studies have demonstrated that treatment of nocturnal seizures can improve sleep quality (Bazil, 2000; Tachibana et al., 1996; Touchon et al., 1987; van Golde et al., 2011).

Seizures and sleep have a bidirectional relationship, such that seizures can change sleep architecture, and certain sleep states can facilitate the occurrence of seizures (Tezer et al., 2014). The two main sleep states, non-rapid eye movement (NREM) and rapid eye movement (REM), have distinct physiological characteristics that are differentially susceptible to seizure activity. Seizures are suppressed during REM sleep, which suggests that asynchronous cell discharge patterns during this stage are less likely to propagate action potentials (Shouse et al., 2000; Frauscher et al., 2016). However, seizures are activated during NREM sleep, suggested to be due to the presence of sleep spindles and slow wave sleep (SWS) providing a state of EEG synchronization (Born, 2010; De Gennaro & Ferrara, 2003; Frauscher & Gotman, 2019; Halász et al., 2019; Minecan et al., 2002). Importantly, sleep-related memory consolidation processes rely primarily on sleep spindle and SWS activity, both of which have been shown to independently correlate with overnight memory retention (Clemens et al., 2005; Clemens et al., 2006; Stickgold, 2005; Van Der Helm et al., 2011). Thus, consolidation and seizure activity are likely to co-occur during the same sleep stage, potentially disrupting normal processes necessary for transferring newly learned information to long-term memory.

Current Studies Fail to Adequately Investigate the Effects of Nocturnal Seizures on Memory

To our knowledge, there are no studies that directly assess the impact of nocturnal seizures on memory. The accumulation of seizures over an extended period (e.g., one

month) has been associated with memory impairment; however, this work includes daytime seizures, with no information on the relative proportion of daytime versus nocturnal seizures (Voltzenlogel et al., 2014). Some studies have shown negative associations between interictal discharges during sleep and memory performance the following day (Chakravarty et al., 2019; Chan et al., 2017; Galer et al., 2015; Lambert et al., 2020; Liu et al., 2016; Zhang 2020), while other studies have failed to demonstrate significant correlations (Ebus et al., 2012; Glennon et al., 2016; Maltoni et al., 2016; Novak et al., 2019; Nissenkorn et al., 2017). Reasons for these inconsistencies have been suggested to be due to cross-sectional and retrospective designs, small sample sizes (median N = 11), heterogeneous patient samples, assessment of epileptic activity that is independently recorded from memory testing sessions, and variations in the type and sensitivity of memory assessment tools (see review by Latreille et al., 2017). One study investigating the correlation between slow-wave sleep and overnight retention provided preliminary evidence that nocturnal seizures can disrupt memory for visuospatial material (Sarkis et al., 2016). However, the use of a non-standardized task and small sample size (n = 3) precluded definitive conclusions.

Need for a Longitudinal Study Design

People with epilepsy are widely heterogeneous regarding factors such as baseline memory abilities, seizure history, underlying pathology, and age of epilepsy onset. Therefore, studies examining memory cross-sectionally are inherently limited in their conclusions because they cannot account for these baseline factors that can significantly influence memory functioning. Longitudinal designs permit a direct measure of change within an individual to minimize confounds and allow for a more reliable assessment of

the effect of nocturnal seizures on memory. However, there are currently no standardized tasks available to assess memory repeatedly within a short time frame to conduct longitudinal assessment of memory after a period of sleep.

Selection of the Word Paired-Associates (WPA) Memory Task

Verbal paired-associates tasks are typically regarded as representative of hippocampal function as they directly assess the formation of new associations (Benson & Feinberg, 1977; Clark et al., 2018; Smith, 2001; Giovanello et al., 2003). Creating associations between items during learning is an essential aspect of memory formation, as the hippocampus has been theorized to play a crucial role in integrating multiple elements of an experience (spatial, temporal, or other associated relationships) to form a unitary representation of memory (Eichenbaum, 2001; O'Reilly & Rudy, 2001). Functional neuroimaging studies have demonstrated that associative encoding is also related to greater hippocampal activation and subsequent memory compared to rote rehearsal of words (Davachi & Wagner, 2002; Jackson III & Schacter, 2004). Thus, a task requiring individuals to make novel associations between stimuli may be more effective in identifying compromised hippocampal function.

Verbal word paired-associate tasks are commonly used in studies of sleep-dependent consolidation, as the susceptibility of verbal paired-associates learning to the effects of sleep deprivation has been well-established (Drummond et al., 2000; Ellenbogen et al., 2006; Lubin et al., 1976; Polzella, 1975; Williams et al., 1966). In patients with epilepsy, left (language-dominant) TLE patients tend to perform worse than right (nondominant) TLE patients on WPA learning tasks (Saling, 2009; Weintrob et al., 2002). However, not all measures of verbal memory are affected by left temporal

seizures. Memory for semantically related word pairs (e.g., “sky-cloud”) found on the commonly used Wechsler Memory Scale-IV (WMS-IV) Paired Associates subtest (Wechsler, 2009) are not sensitive to left temporal dysfunction, as these associations are already well-formed (Soble et al., 2014; Wood et al., 2000). Conversely, memory for unrelated word pairs (e.g., “hair-bridge”) is thought to rely heavily on the hippocampal region (Eichenbaum, 2001).

Patients with left TLE also have reduced performance on verbal list learning tasks (i.e., remembering a list of words) (Mungas et al., 1985; Vaccaro et al., 2018). Although list learning tasks such as the Rey Auditory Verbal Learning Test (RAVLT) are commonly used to differentiate left and right TLE during wakefulness, WPA tasks are more sensitive for the evaluation of memory overnight because they have been shown to require sleep for adequate learning and are more sensitive to sleep disruptions (Wood et al., 2000; Ellenbogen et al., 2006). WPA tasks may also provide a better framework for longitudinal studies, as they are less prone to interference effects after sleep due to the cued recall procedure (Ellenbogen et al., 2006).

Memory Testing: Current Limitations in Overnight Assessment

The ability to test memory following nocturnal seizures is hampered by limitations of traditional assessment tools. Currently available WPA tasks use semantically related words not sensitive to left temporal dysfunction (Cameron et al., 2001; Lustenberger et al., 2015), require advanced vocabulary knowledge and/or are translated to English from other languages (Clark et al., 2018; Marshall et al., 2006; Payne et al., 2012), contain both nouns and verbs differing in imageability (Chiarello et al., 1999), or contain emotionally charged words (e.g., death)—all of which confound

assessment of memory performance. Additionally, WPA tasks thus far have not been developed for repeated, overnight memory assessment. Standardized WPA tasks such as the WMS-IV Paired Associates subtest may only have one to two alternate forms and are not created to assess memory daily, while memory tasks used in longitudinal research are typically not created with comparable alternate forms. A task with multiple alternate forms is necessary for retesting patients within a short period (i.e., daily) to compare memory after nocturnal seizures versus nights without seizures. Tasks assessing memory also require standardization to correct for critical demographic factors such as age and education. The current study aimed to address the shortcomings of current WPA tasks by creating and beginning to standardize five alternate versions of a novel WPA task to allow for the assessment of memory over multiple days.

As the field of psychology is beginning to adapt to advancements in technology, there is an opportunity for neuropsychology to capitalize on the benefits of technological administrative methods (Miller & Barr, 2017). Integration of technology into our current assessment methods can create efficient and low-cost tools, benefiting from built-in standardization via uniform instructions and procedures, thereby reducing data entry errors and eliminating time-consuming scoring methods. A computerized memory task also allows greater accessibility for patients, particularly those who may have limited mobility (including individuals with epilepsy who may not be able to drive), time constraints, or require social distancing.

This project had five main goals: 1) Develop a remote, computerized, multiple-form WPA task for repeated overnight assessment; 2) Pilot this task with healthy participants (Study 1); 2) Begin to standardize the task with normative data from healthy

participants (Study 2); 3) Assess the feasibility and validity of the WPA task in epilepsy patients (Study 3); 4) Use this task to begin to study the extent to which nocturnal seizures disrupt memory consolidation processes during sleep (Study 4).

Patients with epilepsy being evaluated at the Columbia University Medical Center (CUMC) were tested during their EMU admission longitudinally over multiple days. We predicted that TLE patients would have poorer recall on mornings following nocturnal seizures than on mornings following nights without seizures.

Development of a Computerized WPA Memory Task for Repeated Overnight Assessment: Selection of Stimuli

Verbal Word Paired-Associates Task

We developed five alternate versions of a WPA task, programmed using E-prime software, that could be administered remotely or in-person using a computer. The WPA task consists of learning word pairs (e.g., fish – pencil), followed by memory testing with a delayed cued recall task. During the learning phase, each word pair is presented on the screen for five seconds, with an interstimulus interval of one second (Weigenand et al., 2016). The order of the word pair list is randomized for each learning trial to prevent participants from associating words within each list. Following presentation of the full word pair list, there is an immediate cued recall trial. Participants are provided with the first word of each pair ("fish") and asked to type the associated word ("pencil"). There is no time limit for participant responses, although response time is collected as a performance variable. Words that are misspelled are marked as accurate before data analysis. For the pilot study (Study 1), the before-sleep learning and cued recall learning trials were repeated until a score of at least 80% (16 out of 20 words) was reached to

ensure learning (this was later changed to three standard learning trials, described in Study 3). The following morning, after a period of sleep, participants would complete a delayed recall trial. Word pairs are not re-presented during the delayed recall trial. Similar to the cued recall trial, the first word of a word pair is presented, and participants are asked to recall the second word from memory. An illustration of the WPA task procedure is presented in Figure 1.

Stimuli Selection

For the initial stimuli selection, 20 semantically unrelated (Poirier & Saint-Aubin, 1995) word pairs matched for word frequency (Glanzer & Bowles, 1976; Roodenrys et al., 2002) and number of syllables (Baddeley et al., 1975) were identified for each of the five alternate forms of the task (5 forms x 20 word pairs = total of 100 word pairs). All 200 words (i.e., 100 word pairs) are nouns (e.g., fish – pencil) with low emotional valence (i.e., avoidance of death-related words and words that commonly cause feelings of disgust or fear) (Waring & Kensinger, 2009). Word frequency was based on spoken language sourced from English (United States) movies and TV series subtitles, a corpus considered superior in predicting word processing times (Brysbaert & New, 2009; SubtlexUS database lexique.org). Semantic similarity between two words was determined using an online calculator based on Latent Semantic Analyses analyzing word comparisons (lsa.colorado.edu). All pairs had <0.16 cosine similarity score (M = 0.05, SD= 0.03), indicating low semantic similarity between words. Word pairs from each of the five versions are shown in Figure 2.

Bootstrap statistics were used to compare stimuli across the five WPA versions to ensure equivalency amongst the versions. Bootstrap confidence intervals (CI) estimations

used 10,000 permutations and bias-corrected and accelerated (BCa) CIs. The 95% bootstrapped CIs overlapped for the five versions of the WPA task based on word frequency (Figure 3), number of syllables (Figure 4), and semantic relatedness (Figure 5), indicating similarity amongst the versions based on these criteria (see Table 1 for descriptives). As a result, none of the words were modified.

Summary

We completed initial stimuli selection and created five alternate forms of a memory task for the overnight assessment of memory. We carefully selected word pairs to include 200 concrete nouns (100 word pairs) with low semantic relatedness and low emotional valence. Alternate forms were statistically equivalent on critical factors, including word frequency in spoken language, semantic similarity, and number of syllables (Heydari et al., 2023). Following this, we piloted the WPA task with healthy participants in Study 1 to assess task difficulty, feasibility of the procedure, and ensure comparability among forms with regard to performance variables such as accuracy and response time.

STUDY 1: PILOTING THE WPA TASK WITH HEALTHY CONTROLS

Method

Participants

Twenty-six adults (4 men, 22 women, ages 26.12 ± 5.40, 18-42 years; education: 17.08 ± 1.96 years; estimated IQ: 105.81 ± 9.78) were recruited from St. John's University and received course credit for participation. Participants were asked about their neurological, psychiatric, and academic history. Individuals with current Major Depressive Disorder (untreated), Psychotic Disorder, insomnia, learning disorder, head injury, stroke, other neurological disorders, or estimated IQ <70 (as determined subsequently by cognitive testing) were excluded. All were native English speakers, or learned English before age six and educated in English.

Procedure

All procedures were completed remotely through a Zoom video call with research personnel. Participants were randomly assigned to complete one version of the WPA task. Participants contacted research personnel before and after sleep to complete the learning and delayed recall phases of the task. Participants were asked to refrain from writing down word pairs and were watched by research personnel to ensure compliance. During the morning of testing, participants were queried about the number of hours slept and completed the Groningen Sleep Quality Scale to assess subjective sleep quality during the prior night (Jafarian et al., 2008). Lower scores on the Groningen Sleep Quality Scale indicated better subjective sleep (range 0-14). Participants also completed additional measures to enable characterization of the sample and evaluate other factors that may influence memory performance. As recommended in NIH Common Data

Elements, these included: Wechsler Adult Intelligence Scale-IV (WAIS-IV) Matrix Reasoning (nonverbal abstract reasoning) and Vocabulary for estimated IQ (Denney et al., 2015; Wechsler, 2008); WAIS-IV Digit Span Forward for attention, WAIS-IV Digit Span Backward for working memory; Beck Depression Inventory-II (BDI-II; Beck et al., 1996) for subjective depressive symptoms; and Beck Anxiety Inventory (BAI; Beck et al., 1988) for subjective anxiety symptoms.

Hypotheses

As word pairs were shown to be equivalent across versions, we predicted no differences among the five versions for WPA performance variables, including accuracy and response times. Because this was a non-clinical sample with no known sleep or psychiatric disorders, we predicted that subjective sleep quality, number of hours of sleep, and subjective anxiety and depression would not be associated with WPA performance.

Statistical Analysis

We analyzed the pattern of missing data to determine if multiple imputation for missing data was appropriate. There were 27 variables entered into the analysis, and 62 of 640 values were missing (8.83%) related to cognitive test performance variables. There were no missing data related to WPA task performance. We conducted Little's Missing Completely at Random test (MCAR test) and the pattern of missing data was consistent with an MCAR model (Little's MCAR test χ^2 (79) = 65.29, p = 0.87). We elected to impute the missing data with multiple imputation using all the predictors to help predict values for missing data. However, only one imputation dataset was used for the analysis. No outliers were observed.

Variables used to characterize WPA performance were 1) total words learned, 2) average response time during learning trials, 3) number of trials to reach 80% accuracy, 4) number of words remembered for delayed recall, 5) average response time during delayed recall trials, and 6) percent retained (words learned/words remembered). Data distributions were negatively skewed for accuracy variables and positively skewed for response times, indicating high accuracy and fast response times in this healthy and highly educated sample. Thus, we compared performance across the five versions using bootstrapping techniques. Spearman rank correlations and bootstrapping techniques were used to analyze the relations between sleep, cognitive performance, and WPA performance.

Results

The means and standard deviations of performance variables for the five versions are presented in Table 2. Data analysis showed that all 95% bootstrapped BCa CIs of mean group differences included 0, indicating the five versions were comparable in difficulty level based on participant performance. As hypothesized, there were no significant associations between subjective sleep and WPA performance (all *p's* > 0.65, BCa 95% CIs included 0), or hours of sleep and WPA performance (all *p's* > 0.37, BCa 95% CIs included 0). However, most participants slept seven or more hours (n = 22; *M* = 7.81, *SD* = 1.27, range = 4-9), and had sleep scores <=6, indicating good quality sleep (n = 24, *M* = 3.19, *SD* = 2.45, range = 0-8). Self-reported depression and anxiety scores were not associated with WPA performance (all *p's* > 0.34, BCa 95% CIs included 0). Estimated IQ, vocabulary, nonverbal abstract reasoning, attention, and working memory scores were also not correlated with WPA performance (all *p's* >0.24, BCa 95% CIs

included 0).

Study 1 Discussion

We assessed the usability of the task in a group of healthy controls who completed one night (i.e., one version) of the WPA task. In this between-subjects design, we found that WPA task versions were generally equivalent based on performance variables, including accuracy and response times for learning and delayed trials, number of trials to reach 80% criteria, and overnight percent retention. WPA performance was not associated with hours of sleep, subjective sleep ratings, mood, or cognitive performance. For Study 2, we used a longitudinal design to assess WPA performance for each alternate version in a within-subjects design, administering all five versions to each participant over five nights and days.

STUDY 2: LONGITUDINAL ASSESSMENT OF WPA TASK PERFORMANCE IN HEALTHY CONTROLS

Method

Participants

Forty-three healthy adults were recruited via advertising at CUMC and SJU and online advertisements. A telephone screening questionnaire asked participants about their neurological, psychiatric, and academic history. Individuals with current Major Depressive Disorder (untreated), Psychotic Disorder, insomnia, learning disorder, head injury, stroke, other neurological disorders, or estimated IQ <70 (as determined subsequently by cognitive testing) were excluded. We restricted the age range to younger adults (18-55 years) due to greater risk for neurological disorders that can affect older adults (e.g., dementia). Most participants were native English speakers (n=40). Three participants who were not native English speakers were also administered the Bilingual Dominance Scale to quantify language dominance (Dunn & Tree, 2009). Participants received $60 compensation for approximately two hours of participation over five days.

Excluded Participants

Four participants were administered the WPA task with learning trials requiring 80% criteria. Because the task was later changed to a standard 3-trial learning phase (see Study 3 Modification of the WPA Task), these four participants were excluded from the final analysis. One participant was excluded due to a reported diagnosis of insomnia, and another was excluded due to non-native English language dominance based on Bilingual Dominance Scale scores.

The final sample included 37 participants ages 18-55 (M = 24.05, SD = 7.08) with

12-20 years of education (M = 15.05, SD = 2.11) and estimated IQ of 98.38 (SD = 11.80). Thirty-two participants completed all five WPA task versions (morning and night), two participants completed two WPA task versions (morning and night), and three participants missed one morning delayed recall task. Of note, this high participation rate supports the feasibility of the task procedure and ease of use for the longitudinal task procedure, as participants were able to complete the task independently over five days (five mornings and five nights) without the presence of research personnel.

Procedure

Research personnel met with participants remotely via video call at a time before sleep, as determined by the participant. Participants completed learning trials for the first night while research personnel were present through videoconference to answer any questions about study procedures. After the first night, participants were provided links to complete the WPA task independently without research personnel present before sleeping and after waking. The order of test versions presented over five days was randomized for each participant. Participants were asked to refrain from alcohol or substance use for the duration of the study. Each morning, participants completed the Groningen Sleep Quality Scale to assess subjective sleep quality. On a separate day after the five WPA task days, participants also completed cognitive testing that included the tasks from Study 1, as well as the Oral Trail Making Test A to assess processing speed and the Oral Trail Making Test B to assess cognitive flexibility (Mrazik et al., 2010). Participants also completed the Rey Auditory Verbal Learning Test (RAVLT) to analyze convergent validity, a commonly used measure in clinical practice to assess memory (Rey, 1983). The RAVLT consists of an orally presented 15-word list with five learning trials, 3-minute delayed

recall (immediate recall), 30-minute delayed recall, and recognition testing. RAVLT scores were converted to z scores based on age (Schmidt, 1996).

Hypothesis

As suggested by results from Study 1, we predicted WPA performance would be comparable among the five versions in this group of healthy controls completing the task longitudinally.

Statistical Analysis

Before proceeding with the data analysis, all variables were screened for missing data. There were 112 variables entered into the analysis, including demographics, WPA task performance, sleep questionnaires, and cognitive test performance. Out of the 4144 values across 37 participants, 291 values were imputed.

Most imputed data (162 cases) were related to cognitive test performance. We conducted Little's MCAR test on the patterns of missing data, which was consistent with an MCAR model (Little's MCAR test χ^2 (936) = 299.77, p = 1.0). Nonetheless, we elected to impute values rather than remove them from the dataset. We used multiple imputation to replace the missing values using all the predictor variables, but only used one imputed dataset for the analysis. We examined the distributional properties of the variables for skewness and outliers, and winsorized as necessary. The distributions for learning and delayed trial response times were normally distributed. However, as expected, performance data for number of words learned, delayed recall, and percent retention were non-normally distributed (negatively skewed), as most participants performed well. Rather than transforming the data, which is subject to increased sampling error and unintuitive interpretation of coefficients, we used Bayesian analyses to compare task versions, which

have been shown to have greater predictive utility, greater power, and less bias (Martin & Williams, 2017). Bayesian analyses were also used to compare WPA task performance based on day of administration.

We examined associations between WPA versions with Spearman's rank correlations (accuracy and percent retention) and Pearson's correlations (response times). We analyzed the relationship between WPA performance and other cognitive measures with Spearman's rank correlations (accuracy variables), Pearson correlations (response times), and bootstrapping techniques. Composite scores for each WPA performance variable were also created by averaging each performance variable across all five days for each participant (average words learned, average response times for learning trials, average delayed recall, average delayed recall response times, and average percent retained over five days). Repeated measures ANOVAs analyzed whether hours of sleep and subjective sleep quality differed across the five days.

Results

Demographic and Cognitive Data

There were no associations between age or education and WPA composite score performance variables (all *p's* > 0.12 and BCa 95% CIs contain 0). However, the vast majority of participants were under the age of 30 (31 of 37 participants) and highly educated (29 participants either currently in college or greater than college education). Considering the relatively truncated age and high education levels, we did not organize the normative performance data by age or education.

Sleep and WPA Performance

We first assessed whether subjective sleep quality or hours of sleep were

consistent across the five days to determine if sleep variables needed to be used as a covariate for further analysis. Participants reported equivalent levels of subjective sleep quality ($F(4,144) = 0.72$, $p = 0.40$)) and hours of sleep ($F(4,144) = 1.44$, $p = 0.24$)) across the five days. Correlations analyzed hours of sleep and subjective sleep quality and delayed WPA performance (delayed accuracy, delayed response times, and percent retention) for each day. Similar to Study 1, there were no associations between subjective sleep and delayed WPA performance, including delayed correct, delayed correct response times, and percent retained across all five days (all *p's* > 0.30 and BCa 95% bootstrapped CIs included 0). Number of hours of sleep was not correlated with delayed WPA performance (all *p's* > 0.40 and bootstrapped BCa 95% CIs included 0). However, most participants slept seven or more hours each day (Day 1: n = 25, Day 2: n = 28, Day 3: n = 26, Day 4: n = 30, Day 5: n = 27), and had sleep scores <=6, indicating good quality sleep (Day 1: n = 28, Day 2: n = 27, Day 3: n = 31, Day 4: n = 29, Day 5: n = 29).

WPA Task and Cognitive Performance

Spearman's rank and Pearson correlations analyzed WPA composite scores and cognitive performance, including estimated IQ, Vocabulary scaled scores, Matrix Reasoning scaled scores (nonverbal abstract reasoning), Digit Span Forward scaled scores (attention), Digit Span Backward scaled scores (working memory), Oral Trails A z scores (processing speed), and Oral Trails B z scores (cognitive flexibility). Of note, overall estimated IQ was associated with greater words learned ($r_s = 0.50$, $p = 0.002$) and delayed recall ($r_s = 0.33$, $p = 0.05$), and faster response times for learning ($r = -0.47$, $p = 0.003$) and delayed trials ($r = -0.29$, $p = 0.08$), but not percent retention ($r_s = 0.16$, $p = 0.35$). Faster processing speed was also associated with faster response times on learning

(r = -0.32, p = 0.05) and delayed recall trials (r = -0.39, p = 0.01). Although better attention was associated with fewer words learned during learning trials (r_s = -0.32, p = 0.05), this effect was driven by five participants. Correlations between the WPA task and cognitive performance are presented in Table 3.

Convergent Validity

Spearman's rank correlations were used to analyze RAVLT and WPA performance, as RAVLT performance variables were non-normally distributed (healthy participants performed well on this learning and memory measure). Results of Spearman's rank correlations revealed WPA learning accuracy composite score was strongly correlated with RAVLT learning total (r_s = 0.539, p < 0.001, BCa 95% CI 0.316-0.707). WPA delayed recall composite score was correlated with RAVLT delayed recall (r_s = 0.390, p = 0.017, BCa 95% CI 0.157-0.590) and RAVLT recognition scores (r_s = 0.452, p = 0.005, BCa 95% CI 0.117-0.721). WPA task learning and delayed response times were generally not associated with RAVLT performance variables. However, faster learning response times were correlated with better RAVLT immediate recall scores (r_s = -0.30, p = 0.07, BCa 95% CI -0.614-0.051). Correlations between WPA task and RAVLT performance are presented in Table 4.

Comparison of WPA Task Versions

Healthy control performance data comparing the WPA task versions are presented in Table 5. A Bayesian repeated measures ANOVA was conducted to compare performance across the five alternate versions for the final version of the WPA task (i.e., three standard learning trials without 80% criterion). We report Bayesian model comparisons between two competing models: the null model (no differences between the

five versions) and an alternative model (differences between the five versions). We determined probabilities based on the Bayes factor (BF_m), which was used to reflect which model was more likely to be correct based on the data. The five versions were compared based on number of words learned (i.e., words recalled during the final learning trial), average learning trial response times, delayed recall, average delayed recall response times, and percent retained. The model of no differences was strongly supported for all performance variables. All Bayes factors for the alternative model of differences were <0.13, suggesting no differences in performance between the five WPA versions (see Table 6 for Bayesian model comparisons).

Correlations: WPA task performance and versions

Although we determined no statistical differences between the versions, we also examined the strength of the associations between the different versions based on performance data. Results of Spearman's rank and Pearson correlations indicated generally strong correlations between the five alternate versions in relation to number of words learned, learning response times, delayed recall, delayed recall response times, and percent retention. However, version four had poor correlations with versions one, three, and five for delayed recall response times. Correlations are presented in Tables 7-11.

Comparison of WPA Task Performance by Day of Administration

We conducted a Bayesian repeated measures ANOVA to compare WPA task performance based on day of administration, regardless of version. We compared two competing models, with the null model supportive of no differences between days, and alternative model supportive of differences existing between days. The model of no differences was more strongly supported than the alternative model, suggesting no

differences between the days (see Table 12 for Bayesian model comparisons). Furthermore, inspection of means and standard deviations are not supportive of significant practice effects over the five days. We also present performance data for the healthy controls based on day of administration in Table 13.

Study 2 Discussion

We modified the WPA task for usability in the epilepsy population by replacing the trials to criterion during learning tasks with standard three-trial learning. We found that in this healthy sample, all performance variables were statistically equivalent across the versions. Additionally, performance did not differ across days, and participants did not exhibit significant practice effects across the five days. We also determined that WPA task performance was strongly associated with learning and memory performance on a standardized list learning task, the RAVLT, establishing convergent validity with this commonly used memory task. We did not present age- or education-specific normative data due to the limited variability of these factors in our population. We next assessed WPA performance in a group of patients with epilepsy at the EMU.

STUDY 3: LONGITUDINAL WPA TASK PERFORMANCE IN EPILEPSY PATIENTS AND COMPARISON WITH HEALTHY CONTROLS

Method

Modification of the WPA Task

For Study 1, the before-sleep encoding and retrieval phases (learning trials) were repeated until a score of at least 80% (16 out of 20 words) was reached. After screening the WPA task with two epilepsy patients in the EMU, we concluded that patients would likely have difficulty reaching the 80% criterion, limiting the feasibility of this task for patients with epilepsy. Specifically, both participants failed to meet the criteria and discontinued the task early due to fatigue and frustration. Additionally, we found that 4 of 26 healthy subjects from Study 1 reached the 80% criterion after a single presentation of the learning trials, and 11 of 26 reached the criterion after two presentations, which limited the amount of exposure to the word pairs for some participants. As the pilot study determined participants, on average, reached the 80% criterion after 2.5 trials, we therefore modified the task to three standard learning trials without training to criterion.

Design

A longitudinal within-subjects design examined WPA task memory performance over three nights and days. We restricted the study to three days rather than five to allow for higher enrollment rates. Patients with epilepsy admitted to the epilepsy monitoring unit (EMU) were administered the WPA learning task before sleep, and cued recall was tested upon awakening the following morning. Patients were tested with alternate forms of the WPA task over three consecutive days in the EMU, with the expectation that nocturnal seizures would occur on some, but not all, nights. This enabled within-subjects

comparison of memory performance following nights of seizure occurrence to nights of seizure absence.

Participants

Thirty-three patients were recruited from anticipated EMU admissions at CUMC. Inclusion criteria included participants ages 18-55, IQ > 70 (determined from cognitive testing) and no diagnosis of untreated major psychiatric disorder, other neurologic disorder, or known sleep disorders other than mild insomnia. Patients were asked to participate for up to three days, however, because length of stay at the EMU varies based on clinical circumstances, some patients were discharged or withdrew earlier (see Figure 6 for recruitment diagram). Following CUMC IRB regulations, participants were not permitted to receive compensation during their EMU admission. Participants were instead compensated $40 for participation in a follow-up study after hospital discharge, during which they completed the cognitive tasks described in Study 2. Twenty-four participants completed the follow-up study.

Eight participants were excluded from further analyses: two patients who consented to participate did not complete any WPA task (one due to epileptologist recommendation for reasons due to clinical care and one withdrew), two completed the WPA task with 80% learning criterion, three patients were later diagnosed with having psychogenic non-epileptic seizures, and one patient reported using cannabis gummies throughout their EMU stay, which could affect learning and memory. Therefore, the final sample included 25 patients.

Demographic and clinical data

The following information was obtained to characterize patient samples and

analyze memory performance as a function of these demographic and clinical variables: age, education level, occupation, race, ethnicity, type and number of anti-seizure medications, age at epilepsy onset, seizure type(s), seizure frequency, risk factors, presence/type of lesion. Demographic information for the 25 patients is as follows: 13 females and 12 males, age = 29.68 (7.53), age range 18-44, education = 14.92 (2.34), and estimated IQ = 98.86 (16.27). Most participants were right-handed (n = 22). Patients varied in their epilepsy type, although most were characterized as having temporal lobe epilepsy [right temporal (n = 10), left temporal (n = 6), bitemporal (n = 1)], left hemisphere with unclear localization (n = 2), generalized (n = 1), or unknown localization (n = 5).

Procedure

Patients were approached during the day to provide informed consent to participate in the study. Research personnel returned at night to complete the WPA learning trials at the patient's reported bedtime. Patients were provided with a laptop and completed the WPA task as described previously, however, research personnel remained in the room while participants completed the task. Each night, participants were randomly assigned a different version of the WPA task. Participants were informed of the memory task the next day but were asked to refrain from writing down or rehearsing the word pairs when research personnel left.

Patients underwent continuous video-EEG monitoring with standard scalp electrode placement as part of their standard epilepsy unit admission. Type and frequency of nocturnal seizure activity were documented and interpreted as part of patient clinical care. Participants also completed cognitive testing remotely after discharge. They

completed the cognitive tests described in Study 2, as well as the Memory Assessment Clinics Scale for Epilepsy (MAC-E), a 30-item Likert scale evaluating subjective memory concerns (Miller et al., 2020). If participants completed a recent neuropsychological evaluation, tests that were already administered were not re-administered, and scores from the evaluation were used.

Hypothesis

As people with epilepsy generally have poorer memory abilities than healthy individuals regardless of epilepsy type (Tramoni-Negre et al., 2017; see review Novak et al., 2002), we predicted that patients would have poorer WPA performance compared to the healthy controls from Study 2.

Power analysis

We calculated our power analysis based on a between-subjects design (epilepsy versus healthy controls). A sample size of 52 ensured sufficient power (80%) with an alpha level of 5% to detect a large estimated effect size of at least Cohen's d of 0.8.

Statistical Analysis

Similar to the analysis with healthy controls, composite scores for each WPA task performance variable were created by averaging each performance variable across the days they participated. However, the number of days averaged differed across participants. Of the 25 patients, 17 completed all three days of the WPA tasks (morning and night), three completed two days (morning and night), and two completed one day (morning and night). One participant completed three days (morning and night) and one completed two days (morning and night), but the learning trials for one of the days were not saved due to technical difficulties. One participant completed two days but did not

complete one delayed recall task.

The pattern of missing data was analyzed for the 25 patients with epilepsy. Eighty-one variables were entered into the analysis, with 2025 values, and 354 of the values were missing (17.5%). We elected not to impute missing data because there was a high percentage of missing data and missing data were based on missing days (rather than data within a day). However, the pattern of missing data was consistent with an MCAR model (Little's MCAR test χ^2 (1157) = 380.38 p = 1.0). The distributional properties of the variables were examined for skewness, and outliers were winsorized. All performance data variables for patients were normally distributed. Therefore, Pearson correlations examined demographic, sleep, mood, and cognitive data. One-way ANCOVAs with bootstrapping compared WPA performance between healthy controls and epilepsy patients.

Results

Correlations

Estimated IQ, education, and age were not associated with WPA performance variables (all *p's* > 0.19)**.** We compared MAC-E subjective memory to WPA memory performance, and MAC-E subjective memory was not associated with average delayed recall (composite score, r = -0.11, p = 0.69), average delayed response time (composite score, r = -0.11, p = 0.68), or percent retained (composite score, r = -0.23, p = 0.41). However, MAC-E ratings also did not correlate with RAVLT immediate (r = 0.33, p = 0.25), delayed recall (r = 0.32, p = 0.25), or recognition z scores (r = 0.02, p = 0.94), suggesting poor overall subjective assessment of objective memory. When examining subjective memory and mood, MAC-E subjective memory scores were associated with

self-reported anxiety (BAI; r = -0.45, p = 0.08, BCa 95% CI -0.76 –
-0.01) and self-reported depression (BDI; r = -0.50, p = 0.07, BCa 95% CI -0.84-0.09).

Comparison of Epilepsy and Healthy Control Performance

To assess the validity of the WPA task, we analyzed whether WPA task performance would be poorer in a clinical epilepsy population compared to healthy controls. For this analysis, we only examined data from nights when patients did not have nocturnal seizures. Therefore, we excluded data from three patients who only had nights with nocturnal seizures (two patients with right temporal lobe epilepsy and one with unknown epilepsy type). The final epilepsy sample for this analysis included 22 patients (12 females and 10 males). Independent t-tests compared epilepsy and healthy control groups regarding age, education, and estimated IQ. There were no differences in education (epilepsy = 15.0±2.35 and healthy controls = 15.05±2.11, p = 0.81) or estimated IQ (epilepsy = 99.85±16.26 and healthy controls = 93.38±11.80, p = 0.91). However, patients were older (29.45±6.94)) than healthy controls (24.05±7.08), p = 0.004. Thus, age was used as a covariate in the following ANOVA analyses.

We conducted one-way ANCOVAs comparing healthy controls and epilepsy on average WPA task performance with age as a covariate. We compared performance for the first three days for healthy controls, as patients only completed up to three days of the task. However, performance comparing five days of healthy control data produced the same results and are presented in Table 14. When comparing the first three days for healthy controls and patients, healthy controls performed better than patients across all WPA performance variables. Healthy controls learned a greater number of words (M = 16.55, SD = 4.82) than patients (M =12.12, SD = 5.55) and remembered more words the

following day (*M* = 14.75, *SD* = 5.46) compared to patients (*M* = 8.33, *SD* = 5.47). Healthy controls also had faster response times on learning trials (4.29±1.18 seconds compared to 6.26±2.14 seconds) and delayed trials (4.07±1.12 seconds compared to 6.42±2.56 seconds). All bootstrapped *p* values for mean differences were <0.05, partial eta squared effect sizes were >0.08, and bootstrapped BCa 95% CI's did not include 0. Three-day performance data for epilepsy and healthy controls are presented in Table 15.

WPA Performance and Sleep

We examined relations between hours of sleep, subjective sleep quality, and WPA performance for patients on days without nocturnal seizures. WPA delayed recall, response times, and retention were not associated with number of hours of sleep or subjective sleep quality (*p's* > 0.14).

Study 3 Discussion

On days without nocturnal seizures, patients with epilepsy performed worse than healthy controls on all WPA performance variables, supporting the value of the WPA task in assessing learning and memory dysfunction. Subjective memory was not associated with objective memory, although it was associated with mood. We next analyzed patients who had nocturnal seizures to determine whether WPA delayed memory performance (delayed recall, delayed recall response times, and percent retention) was affected by nocturnal seizures, compared to nights when these patients did not have seizures.

STUDY 4: COMPARING DELAYED WPA TASK PERFORMANCE AFTER NIGHTS OF NOCTURNAL SEIZURES VS. NIGHTS OF NO SEIZURES

Method

Participants

Of the 25 patients with epilepsy from Study 3, 18 patients were excluded from analyses for the within-subject analyses comparing nocturnal seizure nights to seizure nights because they had no nocturnal seizures during the three study nights. Three other patients were excluded because they had nocturnal seizures during all three nights, and therefore, comparisons between seizure and no-seizure nights could not be conducted. Thus, the final sample consisted of four patients with epilepsy: three with right temporal lobe nocturnal seizures and one with generalized nocturnal seizures. Demographic data for the four patients was as follows: age = 26.75 (8.85), range 18-39, education= 15.0 (2.58), estimated IQ = 109.0 (11.27).

The four participants were assessed over three days, and nocturnal seizures occurred during one or two study nights. Three participants had nocturnal seizures one night and no seizures the other two nights, and one participant had two nights of nocturnal seizures and one night without seizures. WPA performances were averaged across nights of seizure absence and seizure occurrence to compare two time points (memory performance after nocturnal seizures versus no nocturnal seizures). Participants also differed on the number of nocturnal seizures that occurred at night: one participant had one nocturnal seizure, two participants had two nocturnal seizures, and one participant had three nocturnal seizures within one night.

Hypotheses

We did not expect the number of words learned and learning trial response times to differ between nights with and without seizures, as learning trials were completed before sleep. However, we predicted delayed (i.e., overnight) recall, delayed recall response times, and percent retention would be worse after nocturnal seizures compared to nights without seizures.

Statistical Analysis

Performance variables were created by combining performance from nocturnal seizure nights and nights without seizures. Only four epilepsy participants had data to compare memory after nocturnal seizures and nights of seizure absence. We did a sensitivity analysis and determined we would require an effect size of 1.6 to compare these individuals statistically. As can be seen in Table 16, the actual effect size for comparing delayed recall for these four participants was 0.6. We calculated the number of participants we would need, given a large effect size. We determined that a sample size of 24 ensures sufficient power (80%) with an alpha level of 5% to detect a large estimated effect size of at least Cohen's d of 0.6. Therefore, we did not undertake statistical evaluation of these groups.

Results

Within-Subjects Descriptives: The Effect of Nocturnal Seizures

Because the final sample (n=4) did not meet the results of the power analysis (n=24), we did not conduct any analyses comparing seizure nights versus non-seizure nights. Therefore, we present only descriptive data from these participants. WPA performance for the overall participant sample is reported in Table 16. Although

statistical analyses could not be conducted, means and standard deviations of WPA task performance suggest worse performance after nights of nocturnal seizures. The mean number of words remembered during delayed recall was 9.13±6.19 when participants did not have seizures, compared to 5.63±5.22 during seizure nights. Retention after nights without seizures was 67.81±29.35 compared to 45.91±31.62 after nights with seizures. Individual WPA data for each participant are reported in Table 17. Although we report only descriptive data, it is notable that each participant recalled fewer words and had reduced percent retention after nocturnal seizure occurrence compared to nights without seizures.

GENERAL DISCUSSION

Our goal was to create a psychometrically sound instrument to accurately assess memory after multiple nights of sleep that could be used both clinically and for research in multiple disciplines and populations. Accordingly, we developed a remote, word paired-associates memory task with five alternate forms for repeated overnight memory assessment. We present preliminary normative data for the WPA task, including learning and delayed recall accuracy and response times, as well as feasibility and validity data for use in an epilepsy population. We also provide preliminary data suggesting that nocturnal seizures may disrupt memory consolidation for material learned before sleep, although more definitive conclusions would require a larger study.

We created a novel WPA task with five alternate forms, carefully matched on several factors, including word frequency, number of syllables, and semantic similarity. Word pairs for all five versions consist of neutral nouns with low semantic relatedness. This contrasts with a commonly used word paired associates measure, the WMS-IV Verbal Paired Associates, which includes nouns, adjectives, verbs, and semantically related words, and lacks alternate versions to assess memory over multiple days. While there have been WPA tasks developed for research purposes, these not only lack standardization, but alternate forms of the task were not developed to be comparable versions, and the word pairs lack necessary methodological control of factors that have been shown to affect memory performance (e.g., word frequency in spoken language, low semantic relatedness between words). These factors may explain why the WMS-IV Verbal Paired Associates task has failed to show deficits in early dementia (Pike et al., 2013), while other paired associates tasks have successfully identified impairment in

preclinical Alzheimer's disease in older adults (Blackwell et al., 2003; Fowler et al., 2002; Lowndes et al., 2008). Additionally, to our knowledge, there are no existing word pair tasks that include five alternate forms, specifically created to be used after a period of sleep.

We assessed healthy controls over five days and demonstrated that performance across versions was comparable for all variables, including accuracy, response times, and percent retention. We did not stratify performance data by age or education due to the restricted ranges in this preliminary normative sample. A greater sample size will be necessary to determine whether normative data will require stratification as a function of education and/or age.

The WPA accuracy scores showed adequate convergent validity with the RAVLT learning, delayed, and recognition scores. This result is encouraging as it suggests that the WPA task indeed assesses memory functioning despite the differing format of the task compared to the RAVLT (i.e., cued recall, and words are written rather than orally presented). This result also demonstrates that participants were able to complete the task independently without the presence of an examiner, and further substantiates the reliability and effectiveness of conducting neuropsychological assessments via telehealth methods (Brearly et al., 2017; Cullum et al., 2014; Tailby et al., 2020).

We assessed the validity of the WPA task in a group of patients with epilepsy when they did not have a nocturnal seizure. Consistent with our hypothesis, patients with epilepsy performed worse than healthy controls on all WPA task variables. This suggests that the WPA task can be useful in identifying memory dysfunction in a clinical sample. In patients, subjective memory was not associated with objective memory performance.

This result is not surprising, as relations between subjective and objective memory performance are often weak (Baxendale & Thompson, 2005; Helmstaedter & Elger, 2000). Instead, as supported by prior studies (Rayner et al., 2010; Sabatini et al., 2022), subjective memory was related to mood symptoms.

Memory deficits are a common concern in patients with epilepsy. However, there is little to no research on the impact of nocturnal seizures on memory. We used the WPA task with patients at the EMU to determine whether nocturnal seizures interfere with consolidation of material learned prior to sleep. However, only four patients had data to compare nights of seizure occurrence to seizure absence, precluding statistical analyses. With that caveat, inspection of descriptive statistics suggested that nocturnal seizures appear to be associated with greater difficulty retaining information encoded the night before. This is consistent with our hypothesis that nocturnal seizure can have a deleterious effect on memory recall the next day. We speculate that even when seizures begin outside hippocampal regions, seizure propagation may disrupt hippocampal function in patients who have nocturnal seizures (Liou et al., 2020). To help answer this question, future studies should include EEG analysis from stereo-EEG electrodes implanted in bilateral hippocampal areas. This would enable a more precise analysis of the relation between the nocturnal seizure-involved area and memory functioning, allowing for more direct testing of the hypothesis that disruption of the hippocampus during nocturnal seizures contributes to poor recall the following day. It may also be the case that nocturnal seizures contribute to changes in mood, difficulties with concentration, or fatigue that secondarily negatively affect memory, which future studies would need to consider. Future work may also seek to identify the specific sleep stage

and time of night that the seizure occurred to determine if these factors affect memory performance.

Limitations and Future Directions

Collecting participant data from the EMU presents unique challenges. Firstly, clinical care of EMU patients often involves medication taper and sleep deprivation to increase the probability of seizure occurrence. As both variables can affect memory performance, we attempted to assess patients during days when medication taper and sleep deprivation would be least likely. The CUMC EMU does not typically sleep deprive patients the first few nights following admission, and taper generally does not occur until after the second day. Additionally, the length of stay for each patient at the EMU varies widely (e.g., 1 to 11 days) due to the unpredictability of seizure occurrence. Therefore, we elected to evaluate patients during their first three days of admission to minimize these confounds and increase the likelihood that patients would be able to participate for three consecutive days before discharge. However, we found that assessing patients during the first three days of admission meant they were less likely to have seizures without the common methods of seizure induction (e.g., medication taper, sleep deprivation, flashing lights). Thus, future research may consider delaying participation until the second or third day of admission to increase the probability of capturing nocturnal seizures, utilizing potential medication changes as a covariate in analyses as necessary.

Participants were asked about the time they generally went to bed at night for research personnel to return to complete the task; however, participant estimation was not consistently accurate (e.g., some patients indicated their bedtime as 9:00 pm but reported

the next day they did not sleep until 1:00 am). It would be best if patients were tested immediately before sleep and were able to complete the WPA task on their own without research personnel present. However, there was concern that patients might forget to complete the task or have technical difficulties with the unfamiliar laptop provided to them. Future studies may consider leaving the laptop with the patient to complete the task prior to their actual bedtime, and having research personnel provide cellphone reminders and be accessible through phone for technical difficulties. Because participants indicated their sleep/wake times through a sleep questionnaire, future analyses could determine whether the amount of time between learning trials and sleep affects delayed recall.

It is also important to note that healthy controls completed the WPA task independently, while patients at the EMU completed the task with research personnel in the room. Although the task was initially developed to be completed remotely at the EMU, this was not feasible within the EMU due to concerns about patients with memory difficulties needing to remember to complete the task. Additionally, it is also well known that depression and anxiety are highly prevalent in people with epilepsy (Tellez-Zenteno et al., 2007; Scott et al., 2017), and some participants reported difficulty being at the EMU due to fears of having seizures and having to remain in a hospital room for multiple days. Thus, having research personnel in the room while patients complete the task was important to gauge patient distress prior to completing the task. However, future research could have research personnel remind patients to complete the task remotely, assess level of distress before administration of the task, and/or determine whether there are differences between remote and in-person assessment.

Other Possible Applications of the WPA Task

The WPA task provides additional value by recording response times for learning and delayed trials. Our healthy control population generally performed well on measures of accuracy for the WPA task, while response time performance was more variable. The value in response times has been found in the assessment of word-finding abilities in epilepsy, where delayed response latencies provide greater value than overall accuracy measures (Condret-Santi et al., 2014; Hamberger et al., 2022). It may be the case that mild memory difficulties are not apparent when examinees have unlimited time to respond, and that compared to accuracy, response times may be a more sensitive measure in assessing subtle learning and memory weaknesses.

The WPA also consists of a delayed recall phase that occurs several hours after the learning trials, which is not typical of most memory tasks. The WPA task may be useful in patients with transient epileptic amnesia (TEA) and accelerated long-term forgetting (ALF). TEA is defined as recurrent episodes of amnesia, although performance is often normal on standardized tests of memory (Zeman & Butler, 2010), while patients with accelerated long-term forgetting may learn and retain information normally but forget the information over hours or weeks (Blake et al., 2000; Butler & Zeman, 2008). Because standard memory measures typically test memory retention at intervals only up to 30 minutes, TEA and ALF may remain undetected in clinical practice (Elliot et al., 2014). However, the WPA task might be more sensitive to finding memory deficits in TEA and ALF, as memory is assessed after a more extended period.

The WPA task can also be useful for individuals who have hearing loss. As most memory measures are administered orally, memory assessment can pose significant

challenges for these individuals. When individuals present with hearing impairment, tests are often modified to accommodate the impairment (e.g., presenting words visually), and results are interpreted from non-standardized test administration (Hill-Briggs et al., 2007). Therefore, the WPA task may allow for more accurate interpretation findings due to its non-oral modality for learning and memory compared to other memory tasks.

Conclusions

Although even brief nocturnal seizures can cause prolonged changes in sleep architecture, the cognitive effects of nocturnal seizures are understudied (Foldvary-Schaefer & Alsheikhtaha, 2013). Although preliminary, ours is the first longitudinal study that uses a standardized task of overnight memory in patients with epilepsy. We speculate that using standardized tests within sleep and memory research will allow for a greater understanding of the impact of seizures during sleep on memory in patients with epilepsy. Further research on nocturnal seizures and memory functioning could carry clinical implications for treatment to improve memory for epilepsy patients with nocturnal seizures.

This study lays the groundwork for a unique and clinically needed investigation of the specific contribution of nocturnal seizures on memory. We anticipate that results from this work will ultimately carry significant implications for clinical care. Understanding the extent to which nocturnal seizures disrupt memory, and in whom, can inform the development of appropriate behavioral and/or pharmacological treatment(s) and will provide a framework for effectively counseling and educating patients regarding sleep habits.

Table 1

WPA Task Version Comparisons

WPA Version	Word Frequency	# of Syllables	Semantic Relatedness
1	32.44 (29.85)	1.60 (0.50)	0.04 (0.03)
2	31.83 (29.91)	1.65 (0.54)	0.04 (0.03)
3	30.13 (16.49)	1.57 (0.49)	0.06 (0.04)
4	29.77 (25.27)	1.63 (0.42)	0.06 (0.03)
5	31.46 (30.25)	1.73 (0.55)	0.05 (0.04)

Table 2

Study 1 WPA Task Version Comparisons: Performance with 80% Learning Criterion

WPA Version	N	Trials to 80% Accuracy	Words Learned[1]	Learning Trials RT*	Delayed Recall[2]	Delayed Recall RT*	Percent Retained
1	5	2.00 (1.00)	18.40 (1.82)	6.06 (2.23)	17.00 (2.92)	4.76 (2.13)	91.84 (7.25)
2	5	3.00 (1.00)	18.60 (1.14)	4.65 (1.47)	18.40 (1.82)	4.14 (1.49)	98.94 (8.11)
3	6	2.67 (1.75)	18.17 (0.98)	4.91 (1.31)	16.67 (2.58)	4.30 (1.73)	91.55 (11.66)
4	5	2.80 (1.10)	18.00 (1.58)	5.35 (1.53)	16.80 (2.59)	4.64 (1.96)	93.20 (10.02)
5	5	2.40 (1.14)	18.40 (1.67)	4.69 (0.92)	18.20 (2.05)	4.87 (1.22)	98.75 (2.80)
Total	26	2.58 (1.21)	18.31 (1.35)	5.12 (1.51)	17.38 (2.35)	4.53 (1.62)	94.73 (8.65)

[1]Words Learned: number of words recalled on the last learning trial (night).
[2]Delayed Recall: number of words recalled after a period of sleep (morning).
*Response times (seconds)

Table 3

Pearson and Spearman's Rank Correlations: Associations between WPA Task and Cognitive Performance

		IQ	Vocab	Matrix Reason.	Digits Forward	Digits Back	Trails A	Trails B
Words Learned	r_s	**0.50**	**0.35**	**0.30**	**-0.32**	0.07	0.02	0.09
	p	0.002	0.03	0.06	0.05	0.69	0.89	0.61
Learning Trials RT (secs)	*r*	**-0.47**	**-0.51**	**-0.35**	0.04	-0.03	**-0.32**	**-0.37**
	p	0.003	0.001	0.03	0.80	0.85	0.05	0.02
Delayed Recall	r_s	**0.33**	0.24	0.04	-0.21	0.08	0.20	-0.08
	p	0.05	0.16	0.83	0.21	0.65	0.23	0.63
Delayed Recall RT (secs)	*r*	**-0.29**	**-0.37**	**-0.32**	-0.15	-0.01	**-0.39**	-0.12
	p	0.08	0.02	0.05	0.37	0.94	0.01	0.47
Percent Retained	r_s	0.16	0.13	-0.13	-0.14	0.07	0.26	-0.23
	p	0.35	0.45	0.46	0.40	0.68	0.12	0.16

Table 4

Spearman's Rank Correlations: WPA Task and RAVLT Performance

		Total Learning	Immediate Recall	Delayed Recall	Recognition
Words Learned	r_s	**0.54**	**0.49**	**0.39**	**0.39**
	p	<0.001	0.002	0.01	0.01
Learning Trials RT (secs)	r_s	-0.20	**-0.30**	-0.22	-0.21
	p	0.24	0.07	0.20	0.22
Delayed Recall	r_s	**0.52**	**0.38**	**0.39**	**0.45**
	p	<0.001	0.02	0.01	<0.01
Delayed Recall RT (secs)	r_s	-0.23	-0.24	-0.22	-0.18
	p	0.17	0.15	0.19	0.30
Percent Retained	r_s	**0.38**	0.24	0.26	**0.40**
	p	0.02	0.15	0.13	0.01

Table 5

Study 2 WPA Task Version Comparisons: Performance with Three Standard Learning Trials (Final Version of Task)

WPA Version	Words Learned[1]	Learning Trials RT*	Delayed Recall[2]	Delayed Recall RT*	Percent Retained
1	17.49 (4.36)	4.04 (1.33)	15.46 (5.85)	4.17 (1.72)	89.00 (16.44)
2	16.97 (4.99)	4.07 (1.49)	14.70 (5.98)	4.29 (1.60)	83.13 (22.69)
3	16.95 (5.13)	3.98 (1.44)	14.18 (6.41)	4.08 (1.43)	81.44 (21.94)
4	16.59 (4.77)	4.22 (1.71)	14.41 (5.84)	4.38 (1.47)	86.45 (19.19)
5	16.21 (5.35)	4.21 (1.34)	14.27 (5.72)	4.52 (1.56)	86.23 (19.01)

[1]Words Learned: number of words recalled on the last learning trial (night).
[2]Delayed Recall: number of words recalled after a period of sleep (morning).
*Response times (seconds)

Table 6

Bayesian Repeated Measures ANOVA: Comparison of WPA Task Versions

	Model	P(M)	P(M|data)	BF_m	BF_{10}	Error (%)
Words Learned	Null	0.500	0.922	11.788	1.000	--
	Alternative	0.500	0.078	0.085	0.085	0.455
Words Learned Response Time	Null	0.500	0.971	33.788	1.000	--
	Alternative	0.500	0.029	0.030	0.030	0.546
Delayed Recall	Null	0.500	0.939	15.299	1.000	--
	Alternative	0.500	0.061	0.065	0.065	0.435
Delayed Recall Response Time	Null	0.500	0.954	20.674	1.000	--
	Alternative	0.500	0.046	0.048	0.048	0.714
Percent Retained	Null	0.500	0.886	7.734	1.000	--
	Alternative	0.500	0.114	0.129	0.129	0.400

Null: no differences between versions; Alternative: differences exist between versions

Table 7

Spearman's Rank Correlations: Comparing the Number of Words Learned for the Five Alternate Versions

		Version 1	Version 2	Version 3	Version 4	Version 5
Version 1	r_s	**--**	**0.60**	**0.57**	**0.67**	**0.54**
	p	--	<0.001	<0.001	<0.001	<0.001
Version 2	r_s	**--**	**--**	**0.62**	**0.52**	**0.58**
	p	--	**--**	<0.001	<0.001	<0.001
Version 3	r_s	--	**--**	**--**	**0.50**	**0.58**
	p	--	**--**	**--**	0.002	<0.001
Version 4	r_s	--	**--**	**--**	**--**	**0.72**
	p	--	**--**	**--**	**--**	<0.001
Version 5	r_s	--	**--**	**--**	**--**	**--**
	p	--	**--**	**--**	**--**	**--**

Table 8

Pearson Correlations: Comparing Learning Trial Response Times between the Five Alternate Versions

		Version 1	Version 2	Version 3	Version 4	Version 5
Version 1	*r*	**--**	**0.32**	**0.40**	**0.45**	**0.47**
	p	--	0.05	0.01	0.005	0.003
Version 2	*r*	**--**	**--**	**0.55**	**0.38**	**0.60**
	p	--	**--**	<0.001	0.02	<0.001
Version 3	*r*	--	**--**	**--**	**0.61**	**0.70**
	p	--	**--**	**--**	<0.001	<0.001
Version 4	*r*	--	**--**	**--**	**--**	**0.59**
	p	--	**--**	**--**	**--**	<0.001
Version 5	*r*	--	**--**	**--**	**--**	**--**
	p	--	**--**	**--**	**--**	**--**

Table 9

Spearman's Rank Correlations: Comparing Delayed Recall Accuracy between the Five Alternate Versions

		Version 1	Version 2	Version 3	Version 4	Version 5
Version 1	r_s	**--**	**0.71**	**0.55**	**0.53**	**0.72**
	p	--	<0.001	<0.001	<0.001	<0.001
Version 2	r_s	**--**	**--**	**0.44**	**0.62**	**0.71**
	p	--	**--**	0.007	<0.001	<0.001
Version 3	r_s	--	**--**	**--**	**0.35**	**0.58**
	p	--	**--**	**--**	0.03	<0.001
Version 4	r_s	--	**--**	**--**	**--**	**0.66**
	p	--	**--**	**--**	**--**	<0.001
Version 5	r_s	--	**--**	**--**	**--**	**--**
	p	--	**--**	**--**	**--**	**--**

Table 10

Pearson Correlations: Comparing Delayed Recall Response Times between the Five Alternate Versions

		Version 1	Version 2	Version 3	Version 4	Version 5
Version 1	*r*	--	**0.55**	**0.36**	0.22	**0.48**
	p	--	<0.001	0.02	0.19	0.003
Version 2	*r*	--	--	**0.57**	**0.30**	**0.46**
	p	--	--	<0.001	0.07	0.004
Version 3	*r*	--	--	--	0.21	**0.37**
	p	--	--	--	0.20	0.02
Version 4	*r*	--	--	--	--	0.15
	p	--	--	--	--	0.37
Version 5	*r*	--	--	--	--	--
	p	--	--	--	--	--

Table 11

Spearman's Rank Correlations: Comparing Percent Retention between the Five Alternate Versions

		Version 1	Version 2	Version 3	Version 4	Version 5
Version 1	r_s	**--**	**0.60**	**0.32**	**0.36**	**0.49**
	p	--	<0.001	0.05	0.02	0.002
Version 2	r_s	**--**	**--**	**0.33**	**0.39**	**0.46**
	p	--	**--**	0.04	0.01	0.004
Version 3	r_s	--	**--**	**--**	0.20	**0.33**
	p	--	**--**	**--**	0.24	0.04
Version 4	r_s	--	**--**	**--**	**--**	**0.50**
	p	--	**--**	**--**	**--**	0.002
Version 5	r_s	--	**--**	**--**	**--**	**--**
	p	--	**--**	**--**	**--**	**--**

Table 12

Bayesian Repeated Measures ANOVA: Comparison of WPA Task Performance based on Day Administered

	Model	P(M)	P(M|data)	BF_m	BF_{10}	Error (%)
Words Learned	Null	0.500	0.972	34.718	1.000	--
	Alternative	0.500	0.028	0.029	0.029	0.415
Words Learned Response Time	Null	0.500	0.871	6.748	1.000	--
	Alternative	0.500	0.129	0.148	0.148	0.400
Delayed Recall	Null	0.500	0.960	23.947	1.000	--
	Alternative	0.500	0.040	0.042	0.042	0.714
Delayed Recall Response Time	Null	0.500	0.653	1.882	1.000	--
	Alternative	0.500	0.347	0.531	0.531	0.485
Percent Retained	Null	0.500	0.906	9.603	1.000	--
	Alternative	0.500	0.094	0.104	0.104	0.594

Null: no differences between days; Alternative: differences exist between days

Table 13

Study 2 WPA Task Comparisons based on Day of Administration: Performance with Three Standard Learning Trials

Day	Words Learned[1]	Learning Trials RT*	Delayed Recall[2]	Delayed Recall RT*	Percent Retained
1	16.03 (5.41)	4.63 (1.53)	15.08 (6.04)	3.79 (1.20)	89.42 (17.16)
2	15.92 (6.20)	4.15 (1.41)	14.17 (6.69)	4.11 (1.37)	83.17 (27.17)
3	17.72 (4.09)	4.09 (1.41)	15.00 (5.90)	4.31 (1.59)	84.09 (20.19)
4	17.99 (2.92)	3.87 (1.28)	14.60 (5.23)	4.58 (1.53)	82.10 (19.72)
5	16.26 (5.44)	3.78 (1.52)	14.25 (5.74)	4.62 (1.85)	86.62 (15.19)

[1]Words Learned: number of words recalled on the last learning trial (night).
[2]Delayed Recall: number of words recalled after a period of sleep (morning).
*Response times (seconds)

Table 14

ANOVA with Bootstrapping and Age as a Covariate: Comparing WPA Task Performance in Epilepsy Patients (without Nocturnal Seizures) and Healthy Controls (5 Days)

	Epilepsy	Healthy Control	η_p^2	*p* (bootstrap)	BCa 95% CI[1]	
					Lower	Upper
Words Learned	12.12 (5.55)	16.68 (4.50)	0.09	0.04	0.16	6.50
Learning RT (secs)	6.32 (2.18)	4.17 (1.28)	0.25	0.002	-3.23	-1.05
Delayed Recall	8.33 (5.47)	14.62 (5.18)	0.16	0.002	1.28	7.95
Delayed RT (secs)	6.66 (3.32)	4.29 (1.14)	0.20	0.01	-3.96	-1.20
Percent Retained	64.29 (21.44)	84.03 (16.66)	0.13	0.01	2.15	25.97

[1]Bootstrapped BCa 95% confidence interval mean difference

Table 15

ANOVA with Bootstrapping and Age as a Covariate: Comparing WPA Task Performance in Epilepsy Patients (without Nocturnal Seizures) and Healthy Controls (3 Days)

	Epilepsy	Healthy Control	η_p^2	*p* (bootstrap)	BCa 95% CI[1]	
					Lower	Upper
Words Learned	12.12 (5.55)	16.55 (4.82)	0.08	0.04	0.18	5.94
Learning RT (secs)	6.26 (2.14)	4.29 (1.18)	0.23	0.003	-2.86	-0.99
Delayed Recall	8.33 (5.47)	14.75 (5.46)	0.16	0.007	1.59	8.36
Delayed RT (secs)	6.42 (2.56)	4.07 (1.12)	0.27	0.002	-3.61	-1.30
Percent Retained	64.29 (21.44)	85.56 (16.99)	0.15	0.01	4.27	29.56

[1]Bootstrapped BCa 95% confidence interval mean difference

Table 16

Overall WPA Task Performance in Epilepsy Patients with and without Nocturnal Seizures

	No Seizure	Nocturnal Seizure	Cohen's *d*
Words Learned	14.50 (5.64)	13.13 (5.45)	0.23
Learning RT (secs)	7.67 (2.06)	6.21 (1.22)	0.86
Delayed Recall	9.13 (6.19)	5.63 (5.22)	0.61
Delayed RT (secs)	7.39 (2.73)	6.17 (1.23)	0.58
Percent Retained	67.81 (29.35)	45.91 (31.62)	0.72

Table 17

Individual Participant WPA Task Performance in Epilepsy Patients with and without Nocturnal Seizures

	Participant 1		Participant 2		Participant 3		Participant 4	
	No Sz[1]	Sz[2]	No Sz	Sz	No Sz	Sz	No Sz	Sz
Seizure Type	Right Temporal		Generalized		Right Temporal		Right Temporal	
# of Nocturnal Sz	--	1	--	2	--	2	--	3
Words Learned	18	18.5	7.5	6	12.5	12	20	16
Delayed Recall	18	12.5	6	4	8.5	6	4	0
Percent Retained	100.0	67.5	80.0	66.7	68.0	50.0	20.0	0.0
Learning RT (secs)	5.7	6.3	10.3	7.8	6.3	5.0	8.2	5.6
Delayed RT (secs)	5.3	5.9	9.8	6.7	4.6	7.4	9.6	4.6

[1]No Sz: no nocturnal seizures
[2]Sz: nocturnal seizure

Figure 1

Illustration of the WPA Task

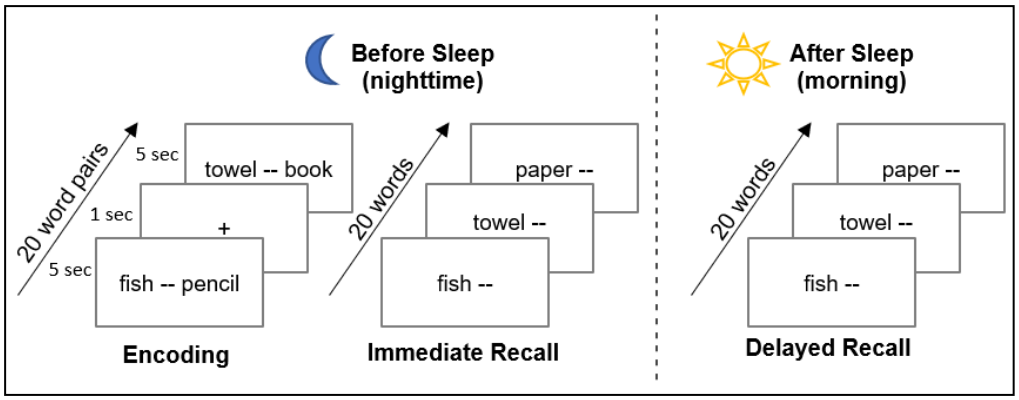


Figure 2

Word Pairs from the WPA Task

LIST 1		LIST 2		LIST 3		LIST 4		LIST 5	
1st Word	2nd Word	1st Word	2nd Word	1st Word	2nd Word	1st Word	2nd Word	1st Word	2nd Word
cloud	purse	boot	dish	bird	ticket	nose	bath	sandal	paperclip
meat	desk	microphone	lizard	bottle	frame	goat	balloon	plant	button
mailbox	broom	jelly	lock	duck	wire	candy	village	magazine	snow
sand	butter	chair	mouse	mountain	roof	flower	wallet	blanket	chicken
wrist	bread	coffee	garden	map	ear	hair	shoe	window	sugar
photograph	tool	winter	bee	penny	juice	lion	pocket	grass	eyebrow
zoo	cotton	needle	lamp	chocolate	coat	letter	star	banana	scarf
hotel	ball	cat	glass	sheep	basket	snail	shampoo	table	music
gift	radio	scissors	nickel	rice	shirt	jewel	umbrella	sock	flame
battery	hammer	helmet	pepper	pencil	train	cup	sticker	motorcycle	robe
envelope	bench	doll	moon	bear	soap	toothbrush	ant	taxi	egg
leg	bank	elephant	bucket	worm	curtain	jet	kitchen	sofa	butterfly
suitcase	cave	corn	tennis	ocean	candle	restaurant	skin	spoon	doorbell
newspaper	stairs	camera	clock	nail	salt	eyelash	bookshelf	machine	hat
cabinet	rainbow	ship	key	telephone	shoulder	knife	coach	bridge	milk
mirror	ladder	fork	street	cake	diamond	oven	fence	thumb	flag
horse	plate	feather	sponge	screwdriver	hanger	museum	forest	tongue	river
cardboard	backpack	lotion	lettuce	lawyer	ice	ketchup	lips	brick	sweater
cheese	king	earring	stapler	library	apple	oyster	barn	stomach	television
fish	ruler	rock	elevator	branch	glasses	carrot	ring	box	tooth

Figure 3

Comparison of Word Pairs in Relation to Word Frequency in Spoken Language

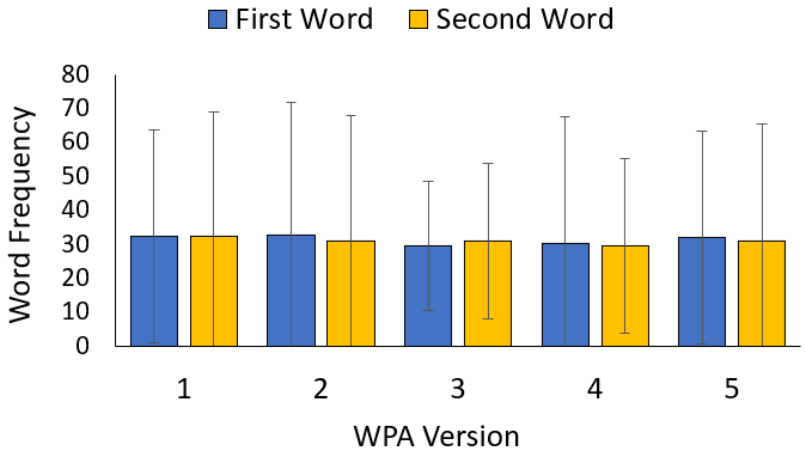


Figure 4

Comparison of WPA Task Versions in Relation to Number of Syllables

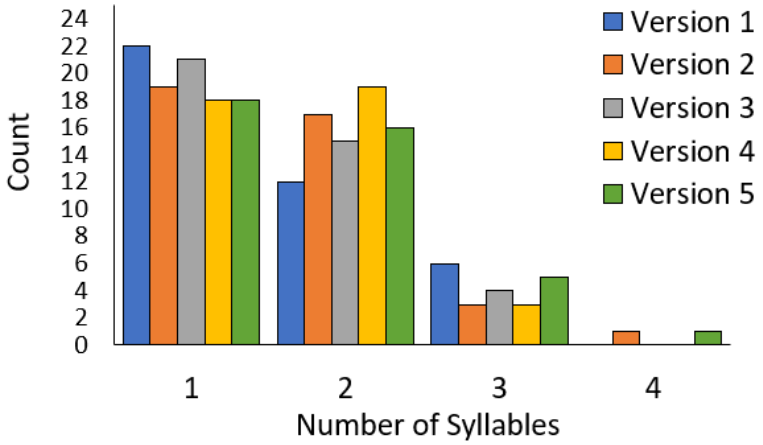


Figure 5

Comparison of WPA Task Versions in Relation to Semantic Similarity between Words

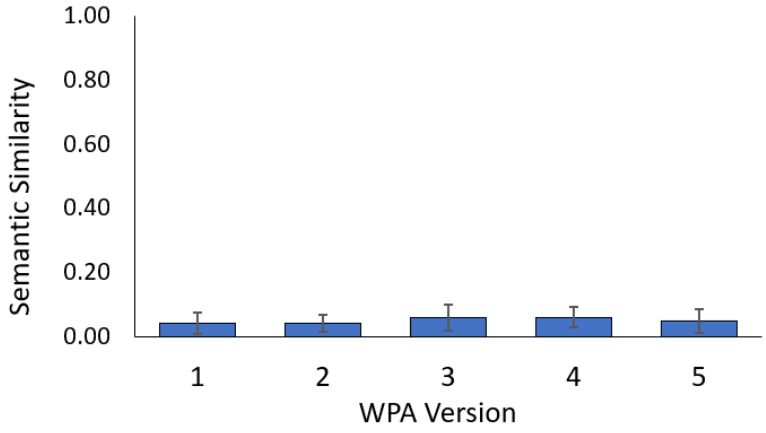
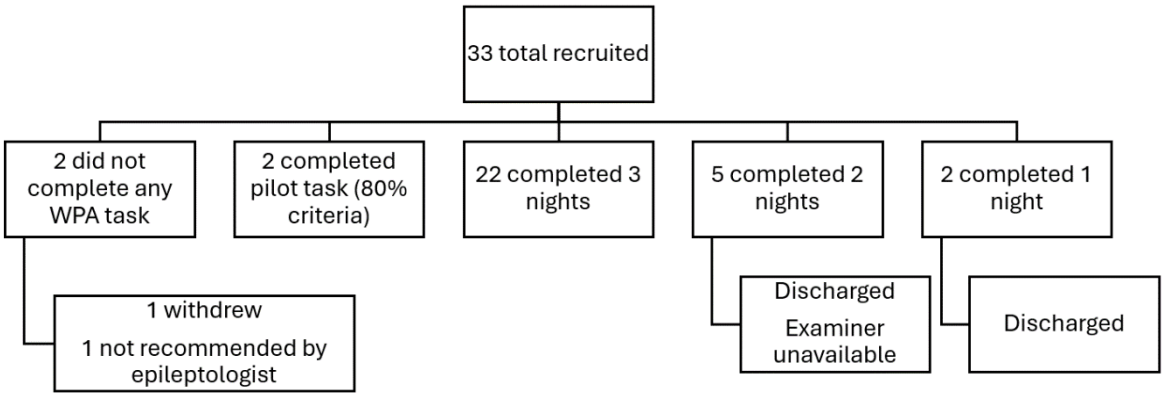


Figure 6

Recruitment Diagram



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Vita

Name	*Nahal Destiny Heydari*
Baccalaureate Degree	*Bachelor of Arts, University of California, Santa Barbara, Major: Psychology*
Date Graduated	*September, 2014*
Other Degrees and Certificates	*Master of Arts, Teacher's College, Columbia University, New York, Major: Psychology in Education*
Date Graduated	*May, 2018*
	Master of Arts, St. John's University, Queens, Major: Clinical Psychology
Date Graduated	*September, 2020*