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Working Memory Intervention in Patients with Temporal Lobe Epilepsy

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Abstract

Memory impairment is a common subjective complaint in those with temporal lobe epilepsy (TLE) and also one of the best-documented performance deficiencies in this population on objective testing. Current clinical interventions do not treat these temporally-mediated memory problems directly. However, empirically validated interventions do exist for the related domain of working memory (WM; the ability to hold new information in mind and manipulate it). Current cognitive models suggest that both declarative and working memory are involved in directing attention to relevant information as well as encoding that information. This bridge between working memory and declarative memory suggests that if working memory can be enhanced, it may enable more efficient everyday functioning. The present study was the first to examine the impact of providing short-term computer-based WM training to patients who have undergone surgery for treatment of medication refractory epilepsy.

The sample consisted of 10 adult post-surgical TLE patients who had either right or left TLE and were at least eight months post surgery and seizure-free. Participants were randomized to either the treatment (N=6) or the active control (N=4) arm of the study. All participants were provided with access to the CogMed QM™ web-based software package, which consists of a variety of activities and tasks that challenge users in areas that require working memory. In the active treatment condition, task difficulty escalated based on increasing ability. Participants in the active control condition completed the same tasks as the other group, but the items stayed at the initial level of difficulty throughout the intervention. Participants completed eight tasks each day, 5 days a week, for 5 weeks.

There was a high degree of acceptability of the training, with 80% of participants completing all or nearly all (>92%) training days. There were no significant differences between
treatment conditions in the direction or magnitude of change for any objective measure of cognitive performance. With all participants taken together, several measures of working memory showed significant improvement between baseline and post-test.

On a self-report measure of functioning on everyday tasks related to executive functioning, those in the active condition displayed significantly greater reductions the severity of their working memory symptoms than did those in the control condition. Taken together, these results provide preliminary evidence that active working memory practice may lead to significant everyday improvement in performance in a cognitive domain that is particularly strongly affected in this patient population. The results also suggest that this type of intervention would be highly acceptable within the epilepsy population, with a high degree of treatment compliance. Within the limitations of the small sample size, these initial findings imply that a computer-based intervention holds promise for treatment for these patients’ working memory dysfunction.
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Introduction

Epilepsy is a neurological condition characterized by recurrent, unprovoked seizures. It affects approximately 65 million people worldwide, and 1 in 26 people in the United States will develop epilepsy at some point in their lifetime (Epilepsy Foundation, 3/2014). Mortality rates in people with epilepsy are two to three times higher than the general population (Forsgren, et al. 2005), and these individuals are substantially more likely to have comorbid medical and psychiatric disorders (Yuen, et al. 2007). In addition to these risks, epilepsy is associated with cognitive deficits in a wide array of domains. Depending on the specific brain regions affected, deficits can be seen in learning, memory, executive functions, language, visuospatial processing, attention, and processing speed (Greener 2013; Lin, et al. 2012). Memory deficits are a particularly common and compelling issue for those with epilepsy (Rausch and Babb, 1993), especially for patients with a seizure origin in the temporal lobe. Indeed, those with temporal lobe epilepsy (TLE) are at the highest risk for memory loss within the epilepsy population (Hoppe, et al. 2007). Working memory, an aspect of executive functioning that refers to the ability to hold new information in mind and manipulate it, is also adversely affected in those with TLE (Stretton and Thompson, 2012; Zamarian, et al., 2011). The current study seeks to evaluate a treatment intervention for these cognitive deficits related to working memory in TLE. The following introduction addresses memory deficits in TLE, working memory in TLE, and currently applied interventions for memory difficulties.

Declarative Memory Deficits in Temporal Lobe Epilepsy

Seizures are commonly classified as either partial (focal), emanating from a localized part of the brain, or generalized, in which the seizure originates from widespread brain regions. Patients with focal epilepsy most commonly have seizures that begin in the temporal lobe
Due to the critical role that temporal lobe brain structures play in memory function, memory impairment is one of the most prevalent subjective cognitive complaints, and also one of the best-documented performance deficiencies on objective testing, among patients with TLE, even in the absence of structural abnormalities (Lee, 2010). Injuries to the temporal lobe, due to developmental abnormality, acquired lesion or injury, surgical excision, or the seizures themselves, have a detrimental effect on memory functioning (Lee, 2010).

Memory studies demonstrate that patients with epilepsy may need more time to learn new information than is typical and then show rapid forgetting of the information over time (Chelune, 1995; Hoppe, et al. 2007; Jansari, et al. 2010; Hermann & Seidenberg, 2007a; Butler & Zeman, 2008). Particularly for patients with TLE, these problems with declarative memory (i.e., impaired verbal learning, deficits in delayed recall, and spatial memory) are prototypical (Elger, et al. 2004; Lee, 2010). Difficulty in novel learning and memory encoding is often material-specific. That is, damage in the language dominant temporal lobe system often presents as a difficulty in encoding new verbal information (Greener 2013; Lin, et al. 2012); dysfunction of the language non-dominant temporal system is evident in deficits with non-verbal, visuospatial functions (Greener 2013; Lin, et al. 2012). Many clinical factors have been associated with poorer cognitive outcomes, such as increased seizure frequency, older age, earlier age at illness onset, treatment with larger numbers of antiepileptic medications, medically intractable seizures, mesial temporal sclerosis, and others (Hendriks, et al. 2004; Hermann, et al. 2006; Hermann, et al. 2007b; Thompson & Duncan, 2005; Hermann, et al. 1992).

**Working Memory Deficits in Temporal Lobe Epilepsy**

In contrast to declarative memory, working memory has been thought historically to be mediated primarily by frontal, not temporal, brain regions (Baddeley, 2010). Working memory
refers to the ability to hold new information in mind and manipulate it. Recent research, however, supports the idea that working memory and long-term declarative memory are not entirely separate constructs and that in fact both utilize medial temporal lobe structures (Ranganath and Bluemenfeld, 2005; Wagner, et al. 2009; Jeneson and Squire, 2012; Nauer, et al. 2015). For instance, current cognitive models suggest that working memory mechanisms play a part in the direction of attention to relevant information, and the encoding and interpretation of that information (Oberauer, et al., 2013). Patients with TLE as a group demonstrate deficits in working memory and executive function in addition to their other cognitive impairments (Stretton and Thompson, 2012; Zamarian, et al., 2011), and they report clinically significant levels of working memory impairment in their daily lives (Fischer, et al. 2015), making the study of working memory critical to a more complete understanding of overall memory functioning in those with temporal lobe epilepsy (Cabeza, et al. 2002; Ranganath, et al. 2003; Campo, et al. 2009). This bridge between working memory constructs and the retrieval and use of long-term memory suggests that if working memory can be strengthened or enhanced, it could potentially enable more efficient use of declarative memory.

**Current Interventions for Memory Deficits in TLE**

There are not currently widely used clinical interventions to reverse declarative memory decrements in this population, and the accepted best practice is to teach strategies that use more preserved cognitive functions to compensate for impaired memory (Dilorio, et al. 2009; Ponds and Hendricks, 2006). For example, some current programs address life skills training such as learning how to utilize calendars and reminders effectively, but they do not focus directly on improving brain function (Dilorio, et al., 2009). Other interventions seek to use cognitive rehabilitation techniques such as individualized mnemonic training, but these interventions must
be individually tailored, and generalization to untrained tasks is either modest or absent (Ponds and Hendricks, 2006).

Like declarative memory, working memory is a domain that substantially impacts everyday functioning (Fischer, et al. 2015). Additionally, in contrast to the paucity of interventions that directly impact declarative memory, there are known working memory interventions that have been reported to improve performance in this domain in children with ADHD (Klingberg, et al. 2002), as well as adults post-stroke (Westerberg, et al. 2007) and with acquired brain injury (Lundqvist, et al. 2010). A growing literature in cognitive neuroscience suggests the importance of working memory to both effective everyday functioning and to memory consolidation; however it is not yet known whether the widespread memory loss that TLE patients experience can be reduced with WM development.

Aside from working memory specific training programs, more general cognitive training programs, such as Lumosity, have been utilized as part of an overall battery of cognitive rehabilitation strategies with both presurgical and postsurgical left TLE participants (Koorenhof, et al. 2012). Participants in the cognitive rehabilitation program were found to improve on one measure of verbal list learning but less in verbal story recall (Koorenhof, et al. 2012). Similarly, it has been found that working memory training in a specific type of task, the n-back training task, can enhance domains such as general fluid intelligence and problem solving (Jaeggi, et al., 2008. However, there are not currently studies looking at the efficacy of these types of working memory interventions in the adult epilepsy population.

The CogMed® QM Program

One example of a commercially available, standardized, computer-based clinical training program for enhancing working memory is CogMed® QM (Klingberg, et al. 2002). CogMed
has been effective in in children with ADHD (Klingberg, et al. 2002), healthy adults (Olesen, et al. 2004), adults post-stroke (Westerberg, et al. 2007), adults with acquired brain injury (Lundqvist, et al. 2010), healthy older adults (Brehmer, et al. 2011), and children with cochlear implants (Kronenberger, et al. 2011). CogMed is a software program that was originally developed in order to train working memory and executive functioning in children with Attention Deficit Hyperactivity Disorder and was later expanded to include an adult version. In examining cognitive treatment strategies, it is always important methodologically to demonstrate that the patients show gains not only on the training test itself but also on untrained tasks; that is, it is critical to show that apparent gains are not explicable solely on the basis of practice effects and, rather, that they generalize to tasks other than those on which the participants receive training. CogMed training has been shown to be associated with improvements in performance of the trained working memory tasks incorporated into the program and, more importantly, with gains on non-trained tasks that also utilized working memory (Klingberg, et al. 2002). This program has been applied in studies that demonstrate gains in working memory achievement in healthy, normal young adult populations (Brehmer, et al. 2012); adults with traumatic brain injuries (Lundqvist, et al. 2010); and adults who have suffered strokes (Westerberg, et al., 2007)

**Aims and Hypotheses**

Working memory training has not yet been studied in the adult postsurgical epilepsy population. The study included postsurgical patients with good seizure control, in order to provide confirmation of seizure localization and to minimize the detrimental cognitive effects of ongoing seizure activity. Additionally, in light of potential hippocampal involvement in WM, inclusion of postsurgical patients allowed us to determine whether working memory could be improved even in those with known mesial temporal excisions. Previous research has focused
on individualized multimodal cognitive rehabilitation strategies for enhancing verbal memory function post-operatively, and has found that post-operative rehabilitation has a promising and positive effect on verbal memory outcome, but that these effects were limited to only those with right TLE surgery (Helmstaedter, et al., 2008)

Online computer-based programs are of particular interest in the epilepsy population, because patients with uncontrolled seizure often have restricted driving privileges that interfere with their ability to participate in interventions that require frequent or daily travel. The CogMed training program specifically is web-based, which allows participants to work on the training using any computer with an internet connection and to complete their daily training in their own home.

Web-based interventions outside of the domain of cognitive retraining have been utilized with the epilepsy population and have met with mixed results. A web-based epilepsy life skills website had training completion rates of 43%, while a web and phone based program for depression among the epilepsy population had completion rates of 30% (Dilorio, et al., 2009; Thompson, et al., 2010). We anticipated that this program would be well received by the patient population and exceed those rates, as it addressed a cognitive domain that is a primary concern and prominent impairment in these individuals.

This study applied the CogMed QM with a post-surgical epilepsy population with the goal of improving working memory function. We hypothesized that participants in the active treatment condition of the training program would display higher gains between pre-test and post-test on objective measures of cognitive function than would those assigned to a control condition. Additionally, we anticipated that participants in the active treatment condition would display a dose-dependent relationship between number of days of treatment completed and their
change between pre-test and post-test scores. Finally, we examined the degree of participant
compliance with the intervention.

Method

Participants

Participants were 10 post-surgical patients with temporal lobe epilepsy ($N = 4$ right
temporal lobe epilepsy; $N = 6$ left temporal lobe epilepsy) who were randomly assigned to either
an active treatment ($N = 6$) or control ($N = 4$) condition.

Participants were drawn from individuals who had undergone temporal lobectomy for
intractable epilepsy at the Epilepsy Center at the University of Cincinnati Neuroscience Institute.
Participants were identified through referral from the epileptologists and psychologists treating
patients at the Epilepsy Center as well as from previous participants enrolled in studies within
the Neuropsychology and Social Cognition Laboratory at the University of Cincinnati who
agreed to be contacted for future research. Additional inclusion criteria included seizure freedom
or well-controlled seizures post-surgically, being between the ages of 18-60, having daily access
to a computer with an internet connection, and being eight months or more post surgery. Waiting
until eight months following surgery allows for stabilization of cognitive functioning, avoids
acute post-surgical effects, and establishes a history of seizure control.

Potential participants were excluded if they had bilateral seizure foci or bilateral
structural abnormalities, medication regimens that had not been stable for at least 5 half-lives at
their entry into the study; neurological disorders other than epilepsy; serious medical conditions
that could affect cognition; serious psychiatric disorders; serious developmental disorders such
as intellectual disability or autism; or documentation of photosensitive seizures.

Procedure
A phone screen, which took approximately five to ten minutes, was utilized to assess study eligibility criteria. Once prospective participants passed the screening process, they were invited to participate in a baseline visit. After providing written, informed consent, participants completed the neuropsychological measures listed below and were randomized into either the active treatment arm or the active control arm of the study, with participants blinded to their study condition. The participants practiced logging into the training program as well as completing practice repetitions of each of the twelve tasks in the program with a member of the study staff using a set of instruction prompts created for this study. Then, in conjunction with study personnel, they created a personalized calendar with a plan for completing the CogMed training sessions for each week of the study period. If the participant missed 2 consecutive days of planned CogMed sessions from this calendar, they were contacted either by e-mail or phone by study personnel to answer any questions and provided a reminder to complete their scheduled training. Participation was monitored through the online CogMed system, which tracked dates and length of time spent training for each participant. At the completion of the baseline visit, participants were compensated $25 for their time and effort. After 5 weeks, the neuropsychological tests from the baseline visit were repeated, and participants were compensated an additional $75 for their time and effort for an overall total of $100 to complete the entire study process. The Institutional Review Board at the University of Cincinnati approved all aspects of this study. A total of 21 participants were screened over the phone, of which 6 declined to participate, due to either a lack of time to complete the training or a lack of a home computer and internet connection. Of the 15 who agreed to participate, 5 were lost to follow-up prior to study enrollment visit.

**Working Memory Training Intervention**
CogMed QM is a software package that consists of a variety of working memory based activities. This software package is web-based and can be accessed by the participants from any computer with a standard internet connection. The QM package includes twelve different tasks, eight tasks assigned each day in a fixed order over the course of twenty-five training days. Each of these tasks focuses on training a specific aspect of working memory.

**Visual Span Tasks**

This set of tasks present visual information and the participant respond in the same sequence as the targets, testing the participants’ visual span. These tasks are: *Cube*, a three dimensional cube is presented on which discs light up in order and the participant is asked to click on the discs in the same order; *3D Grid*, the interior of a three-dimensional cube is presented in which discs light up in order and the participant is asked to click on the discs in the same order; *Grid*, a panel of sixteen square buttons is presented, is lit in a particular order, and the participant is asked to click on them in a corresponding sequence.

**Visual Span Tasks with Stimulus Movement**

Other visual span tasks require participants to respond to stimuli in the same way, but they are required to take into account movement components. These tasks are: *Twist*, a grid of sixteen square buttons are rotated and buttons light up in a particular order, and then the panel rotates back to its original position and the participant must click on those that had been lit in sequence; *Chaos*, several figures are moving across the screen, some of which are lit up in a particular order, and the participant is asked to click on them in the same order; *Rotating*, a series of nine buttons continuously move in a circular pattern, these buttons light up in a particular order, and the participant must click on the buttons in the same way (Rotating).

**Auditory Span Tasks**
Some tasks involve an auditory component and ask participants to respond in either the same order or the reverse order in which stimuli are presented. These are: *Numbers*, a participant hears an auditory list of numbers while observing those numbers lit up on a number pad and then selects those numbers on the number pad in reverse order; *Hidden*, identical to *Numbers* except that no number pad is visually present during stimuli presentation, and the information is only relayed through auditory cues; *Assembly*, a series of bubbles is presented and a string of letters is heard out loud. Each time a letter is heard, a bubble lights up. The participant is asked to remember which letter went with each bubble, and to select that letter from the choices that appear next to each bubble. Finally, *Letters*, nine bubbles surround a central large bubble in the center of the screen. A series of bubbles lights up and, as each bubble is lit, a letter is heard. At the end of the sequence, one of the presented letters will be displayed in the center bubble and the participant must select the bubble that corresponded with that letter.

**Sequencing Tasks With and Without Motor Inhibition**

The program offers two sequencing tasks, one with and one without motor inhibition. *Sort*, a grid of sixteen squares is presented and some of those panels flip to reveal numbers, and then the numbers disappear. The participant is asked to sort these numbers and click on them in order from lowest number to highest number; and *Pop-up*, in which a series of buttons appears on screen in a certain order, which the participant must recreate after seeing the entire sequence by moving their mouse to the first button, inhibiting their response and waiting for the button to change color, then clicking that button and moving on to the next button in the sequence (Pop-Up).

Completing these tasks took approximately 40-60 minutes each day, and the exercises were to be completed 5 days a week for 5 consecutive weeks, for a total of 25 training days.
This training regimen was established and defined by the publishers as a participation and exposure level at which improved working memory outcomes were observed in previous work. After completing the 5-week program in their homes (or after 5 weeks had passed with partial completion), participants returned for post-testing within one week or as soon after that point as was possible. The CogMed program actively tracks performance in real time. The program records the amount of days it is utilized, the amount of time spent each day, and the time spent on each specific task.

**Active Treatment Condition.** The CogMed program tracked the performance of the active treatment participants and increased or decreased the item difficulty as necessary to provide a consistently challenging environment for the participant. This increase or decrease in difficulty is defined by the computer program as a change in the length or amount of information encountered in a task. For example, during the Numbers task, an active treatment participant would hear increasingly longer strings of digits; if they became unable to complete strings of a certain length, the program would titrate downwards until the participant was again successfully completing each task. Participants began at a span of 3 stimuli for each task. In the upper right corner of the screen, the participants were shown their average score on each task, as well as their maximum string length for each task, and they were able to track their own progress. The active treatment also allowed for instructions to tasks to be requested and re-presented as needed by the program.

**Active Control Condition.** The control condition participants completed the same tasks in the same frequency and in the same schedule as the active treatment condition. In this study arm, regardless of task performance, the program never increased or decreased the difficulty of any task: the string length was fixed at three items of information. The control condition did not
receive any feedback from the program with regards to their performance, and did not have access to instructions for the tasks beyond what was provided by study staff at the initial baseline visit. (This limitation was a constraint of the version of the control task provided by Pearson Corporation.) Because participants in this condition did not have access to task instructions from the program during the training period, all participants in both conditions were given a written set of brief instructions for each task at the baseline visit. This procedure was added in order to control for any differences in training that may be due to confusion or misunderstanding about how to complete the task in the control condition, rather than ability to complete the tasks.

**Measures**

At the baseline and post-test visits, participants complete a series of tests that assessed their working memory function in areas that were directly related to the training program as well as areas that were more distally related to the training. They also completed self-report questionnaires that assess everyday functioning on working memory mediated tasks as well as current depressive symptoms, in order to control for any cognitive change that may be caused by depressive symptoms rather than the training program. The baseline and post-test batteries were administered by a trained research assistant who was blinded to the participant’s assigned condition; the randomization, tracking of progress with CogMed, and responses to any questions the participants had were performed by the Principal Investigator, who was not blinded to condition.

In order to measure objective cognitive performance, we utilized several neuropsychological tests similar to those that have been administered in previous published CogMed studies (Westerberg, et al., 2007; Brehmer, et al., 2009; Brehmer, et al., 2011). All of the neurocognitive measures in the present study are standardized, norm-based tests that are
known to be sensitive to neuropsychological deficits in patients with epilepsy. Performance on these tasks required the same cognitive skills as those used in the CogMed program (criterion tests) and those that required similar but differing abilities (near-transfer tasks), as well as tasks that assessed general working memory function (generalizability tasks). The goal was to measure whether the program improved working memory through practice and repetition (criterion tasks) and also to examine whether or not the gain in training effects generalized to other domains (near-transfer and generalizability tasks).

**Neuropsychological Tasks**

**Criterion Tasks.** The criterion tasks consisted of the Visual Memory Span Forward test and the Digit Span Backward test (Brehmer, 2012). These tests were designated criterion tasks because the Digit Span Backward requires the same cognitive skills as the Numbers and Hidden tasks from the program, while the Visual Memory Span Forward is similar to the Cube, 3D Cube, and Grid tasks. For the Visual Memory Span Forward, the examiner used a wooden board with raised blue wooden blocks and touched the blocks in sequences of increasing length [WAIS-Rni (Wechsler, 1981)]. The participant must reproduce the sequences. For Digit Span Backward, the participant must repeat digits in the reverse order they are verbally presented to them by the examiner [WAIS-IV (Wechsler, 2008)].

**Near-Transfer Tasks.** The near-transfer tasks consisted of the Visual Memory Span Backward test, the Digit Span Forward test, and the Digit Span Sequencing test (Brehmer, 2012). For the Visual Memory Span Backward, the examiner used a wooden board with raised blue wooden blocks and touched the blocks in sequences of increasing length, which the participant must reproduce them in the reverse order [WAIS-Rni (Wechsler, 1981)]. The Digit Span Forward test asked participants to repeat digits in the order they are verbally presented by the
examiner [WAIS-IV (Wechsler, 2008a)]. The Digit Span sequencing test asked participants to take digits that are verbally presented and put them in order from lowest digit to highest digit [WAIS-IV (Wechsler, 2008a)]. These tasks are similar to the tasks practiced in the QM program, but there are no direct correlates of Visual Memory Span Backward, Digit Span Forward, or Digit Span Sequencing utilized in the training program.

**Generalizability Tasks.** Participants also completed the Letter-Number Sequencing and Arithmetic tests from the WAIS-IV (Wechsler, 2008), which required the participant to repeat combinations of letters and numbers and to solve mathematical problems respectively.

For the criterion, near-transfer and generalizability measures, scores are measured by raw total of correct answers, with higher number indicating better performance. The Working Memory Index is a reliable and well-normed index of working memory from the WAIS-IV generated from all of the Digit Span tests and the Arithmetic test and adjusted for age, and provides a more stable and standardized method to measure cognitive gain in working memory related tasks. These tests are sensitive to those changes in working memory we are assessing and are accepted as a standard measurement for this area with a high degree of reliability and validity (Jones-Gotman, et al. 2010).

**Premorbid IQ Estimate.** The American National Adult Reading Test [AmNART (Grober and Sliwinski, 1991)] was completed by the participant at the baseline visit. This task required the participant to read aloud an increasingly difficult list of irregularly spelled words from a card in front of them. This measure is commonly used to estimate pre-morbid intellectual functioning, and was applied in the present study to describe the participants’ overall verbal intellectual abilities and to allow examination of possible differences between conditions in overall cognitive functioning.
Self-Assessment of Executive Functioning. The Behavior Rating Inventory of Executive Function – Adult Version [BRIEF-A (Roth, Isquith, and Gioia, 2005)], which is a subjective measure of everyday functioning on tasks requiring executive functioning, including working memory, was administered at both the baseline and post-test visits.

Mood. The Beck Depression Inventory – Second Edition [BDI-II (Beck, Steer, and Brown, 1996)] was administered to evaluate the level of depressive symptomatology. This is a self-report measure, and was administered in order to control for the well-documented effects of depressive symptoms on cognition.

Statistical Analyses

Because of the final sample size and data distributions, assumptions of homogeneity of variance were not met for several key factors (Levene’s t test, p > .05) such as baseline Digit Span scores, post-test Arithmetic scores, post-test Working Memory Index scores, days of training completed and handedness within each condition. In order to examine the data without making assumptions about their distributions, two non-parametric tests, the independent sample Mann-Whitney U test and the Wilcoxon signed-rank test, were used to assess for differences between conditions at baseline and in change scores and to assess the relationship between baseline and post-test scores. The Mann-Whitney U test is a non-parametric test used to evaluate whether the ranks of two independent samples differ significantly from each other. The Wilcoxon signed-rank test is a non-parametric paired difference test that takes into account both direction and magnitude of differences between pairs of scores. Additionally, chi-square tests were used to examine whether dichotomous demographic variables differed significantly in frequency across the two treatment conditions. The original data analysis plan included utilizing parametric tests to assess the interaction between condition and visit, but we were not able to
conduct this analysis. Instead, we investigated group effects at baseline and group effects in the change scores between baseline and post-test (calculated as a difference score), as well as group differences in change scores of self-report of everyday working memory functioning (BRIEF-A), using Mann-Whitney U tests. We assessed the main effect of time utilizing the Wilcoxon signed-rank test. We utilized raw scores for our neuropsychological variables rather than the norm-referenced standardized scores, as the conditions did not significantly differ based on age, the primary analyses were of within-subjects change and, with our small sample size, the increased variability in raw scores is useful for detecting change in score.

Unstandardized effect sizes in the pairwise comparisons of baseline and post-test scores were computed using the probability-of-superiority (PS) (Grissom and Kim, 2012). This approach assesses the probability that in a randomly sampled pair of scores, the score from one specified condition will be greater than the other condition. For the present study, this was calculated as the probability that a participant’s score from the post-test visit would be greater than his or her score from the baseline visit. Two methods exist for assessing tied scores (in the present case, no change between baseline to post-test). One method, a one-against-the-others approach, involves discarding ties and thus reducing the overall sample size, while another method is the one-against-all approach, in which any ties are added by half to the numerator and the overall N remains the same (Brunner and Puri, 2001). We chose the second of these methods, the one-against-all approach, because retaining participants who did not change over time allowed us to evaluate the most clinically relevant estimate of the probability that an individual participant would show positive change due to treatment.

**Results**

**Demographic Comparisons Across Treatment Conditions**
There were 6 participants in the active treatment condition, 3 LTLE and 3 RTLE (66.7% female, $M_{age} = 41.5$ years, $SD = 9.85$). The racial composition was 100% Caucasian and 100% right-handed. In terms of education, one participant had less than a high school education, one had a high school diploma, one had a 2-year college degree, two had a 4-year college degree, and one had completed a graduate degree. Participants in the active condition had a median AmNART score of 110.24, a value that falls within the high average range of intellectual performance.

There were 4 participants in the control condition, all LTLE (75% female, $M_{age} = 42$ years, $SD = 7.66$). The racial composition was 75% Caucasian and 25% African-American. Three participants were right-handed and one was left-handed. In terms of education, one had a high school diploma, one had completed some college education, and two had 4-year college degrees. The control participants had a median AmNART score of 103.52, which is in the average range.

A series of independent sample Mann-Whitney U tests failed to identify significant group differences in age, years of education completed, depressive symptoms, or estimated premorbid IQ ($p > 0.286$ for all comparisons). Chi-square analyses did not identify statistically significant frequencies across treatment condition in gender ($X^2 = 0.079, p = .778$), race ($X^2 = 1.667, p = .197$), handedness ($X^2 = 1.667, p = .197$), or surgical lateralization ($X^2 = 2.857, p = .091$).

**Group Differences at Baseline**

A series of independent sample Mann-Whitney $U$ tests compared the conditions at baseline on all cognitive tasks, to assess possible differences in ability prior to treatment onset. None of the group differences approached statistical significance ($p > .201$ for all comparisons). See Table 1 for median scores at baseline by condition.
Group Differences in Change Scores

No significant differences were identified between the active and control conditions in the direction or magnitude of change (difference scores between baseline and post-test) for any measure of cognitive performance ($p = .257$ or greater for all comparisons). See Table 1 for medians at baseline and post-test.

Main Effect of Time

Because there were no group differences in cognitive change scores, the conditions were collapsed together to assess the effect of time on cognitive performance. With all participants taken together, Working Memory Index, Digit Span Backward raw score, Digit Span Sequencing raw score, and Digit Span Total raw score all showed significant improvement between baseline and post-test. Arithmetic, Letter-Number Sequencing, Visual Span Forward, and Visual Span Backward scores did not change significantly over time. Results for this analysis are presented in Table 2.
Table 1.

Neuropsychological Test Scores: Medians by Treatment Condition

<table>
<thead>
<tr>
<th></th>
<th>Active Treatment (n = 6)</th>
<th>Control Treatment (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post-Test</td>
</tr>
<tr>
<td>Median</td>
<td>Median</td>
<td>Median</td>
</tr>
<tr>
<td>Digit Span Forward Raw</td>
<td>11.50</td>
<td>10.50</td>
</tr>
<tr>
<td>Digit Span Backward Raw</td>
<td>9.00</td>
<td>9.50</td>
</tr>
<tr>
<td>Digit Span Sequencing Raw</td>
<td>8.50</td>
<td>9.50</td>
</tr>
<tr>
<td>Digit Span Total Raw</td>
<td>30.50</td>
<td>31.00</td>
</tr>
<tr>
<td>Arithmetic Raw</td>
<td>12.00</td>
<td>13.50</td>
</tr>
<tr>
<td>Letter-Number Sequencing Raw</td>
<td>19.00</td>
<td>20.00</td>
</tr>
<tr>
<td>Working Memory Index</td>
<td>96.00</td>
<td>104.00</td>
</tr>
<tr>
<td>Visual Span Forward Raw</td>
<td>7.50</td>
<td>8.00</td>
</tr>
<tr>
<td>Visual Span Backward Raw</td>
<td>8.00</td>
<td>7.00</td>
</tr>
</tbody>
</table>

**Group Differences in Span Length Change scores**

The analyses above of Digit Span raw scores evaluated the total number of items correct across trials, regardless of the span length. To examine the clinical relevance of the significant changes in Digit Span raw scores over time, we recorded the longest span length achieved (i.e., the greatest number of digits each participant could recall) for Digit Span Forward, Digit Span Backward, and Digit Span Sequencing. Only Digit Span Backward span length showed significant change over time (Z = -2.310, p = .021, PS = 0.85). Qualitatively, the median score of backwards span length increased by one digit (range = -1 to 2), and 80% of participants displayed at least a one-digit increase in maximum backward span length. These data are presented in Table 2.
Table 2.

Neuropsychological Test Scores Across Conditions.

<table>
<thead>
<tr>
<th></th>
<th>Participants (n = 10)</th>
<th>Wilcoxon Signed-Rank Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Median</td>
<td>Post-Test Median</td>
</tr>
<tr>
<td>Digit Span Forward Raw</td>
<td>10.00</td>
<td>10.00</td>
</tr>
<tr>
<td>Digit Span Backward Raw</td>
<td>8.50</td>
<td>10.00</td>
</tr>
<tr>
<td>Digit Span Sequencing Raw</td>
<td>9.50</td>
<td>10.00</td>
</tr>
<tr>
<td>Digit Span Total Raw</td>
<td>29.00</td>
<td>30.00</td>
</tr>
<tr>
<td>Arithmetic Raw</td>
<td>12.50</td>
<td>14.00</td>
</tr>
<tr>
<td>Letter-Number Seating Raw</td>
<td>19.50</td>
<td>21.00</td>
</tr>
<tr>
<td>Working Memory Index</td>
<td>97.00</td>
<td>100.00</td>
</tr>
<tr>
<td>Visual Span Forward Raw</td>
<td>7.50</td>
<td>8.50</td>
</tr>
<tr>
<td>Visual Span Backward Raw</td>
<td>7.50</td>
<td>8.00</td>
</tr>
<tr>
<td>Digit Span Forward Span Length</td>
<td>6.50</td>
<td>6.00</td>
</tr>
<tr>
<td>Digit Span Backward Span Length</td>
<td>4.50</td>
<td>5.50</td>
</tr>
<tr>
<td>Digit Span Sequencing Span Length</td>
<td>6.00</td>
<td>6.50</td>
</tr>
</tbody>
</table>

*p < .05.

Acceptability

All but one participant in the control condition completed all 25 training days. The remaining participant completed 24 of a possible 25 training days and came in to be seen for post-test on the 25th day due to scheduling conflicts; therefore, this individual did not have the opportunity to complete all possible training days. In the active condition, 3 of 6 participants completed all 25 training days, with the additional 3 completing 92%, 56%, and 40% of possible training days respectively.
**Qualitative Analysis of Relationship Between Compliance and Change Scores**

Due to the high percentage of participants who fully completing the training, we cannot test the hypothesis that change in scores is related in a dose-dependent manner to number of days trained. Figures 1a-d provide information about where those with lower compliance rates (70% - 40%) fell on those cognitive measures that showed significant change over time. It is noteworthy that one participant who had completed only 40% of the training still showed improvement in Digit Span Backward, Digit Span Sequencing, and Digit Span Total.

**Group Differences in Everyday Working Memory Function**

A series of independent sample Mann-Whitney $U$ tests compared change scores for each of the 9 BRIEF-A subscales between baseline and post-test, to assess possible differences in everyday working memory function outcomes. A significant difference between the active and control condition was found for both the Initiate and the Working Memory subscales, with the active condition displaying significantly greater reduction in symptom severity than the control condition, although all participants who endorsed clinically meaningful levels of working memory difficulty at baseline (T-scores $>65$) remained clinically elevated after treatment. These data are presented in Table 3. Figure 2 illustrates the changes that individual subjects reported on the Working Memory subscale of the BRIEF-A.
Table 3.

Self-Report of Executive Functioning by Treatment Condition

<table>
<thead>
<tr>
<th>BRIEF subtest T-scores</th>
<th>Active Treatment (n = 6)</th>
<th>Control Treatment (n = 4)</th>
<th>Mann-Whitney U test</th>
<th>Difference scores for change over time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post-Test</td>
<td>Baseline</td>
<td>Post-Test</td>
</tr>
<tr>
<td>Inhibit</td>
<td>Median</td>
<td>Median</td>
<td>Median</td>
<td>Median</td>
</tr>
<tr>
<td>Shift</td>
<td>54.0</td>
<td>57.0</td>
<td>62.0</td>
<td>62.5</td>
</tr>
<tr>
<td>Emotional Control</td>
<td>61.0</td>
<td>60.0</td>
<td>62.5</td>
<td>61.5</td>
</tr>
<tr>
<td>Self-Monitor</td>
<td>59.5</td>
<td>53.5</td>
<td>57.5</td>
<td>48.5</td>
</tr>
<tr>
<td>Behavioral Regulation Index</td>
<td>63.5</td>
<td>62.5</td>
<td>65.5</td>
<td>62.0</td>
</tr>
<tr>
<td>Initiate</td>
<td>66.5</td>
<td>60.5</td>
<td>57.0</td>
<td>54.5</td>
</tr>
<tr>
<td>Working Memory</td>
<td>83.5</td>
<td>75.5</td>
<td>80.0</td>
<td>80.5</td>
</tr>
<tr>
<td>Plan/Organize</td>
<td>68.5</td>
<td>64.5</td>
<td>66.5</td>
<td>61.5</td>
</tr>
<tr>
<td>Task Monitor</td>
<td>60.5</td>
<td>65.0</td>
<td>60.5</td>
<td>61.5</td>
</tr>
<tr>
<td>Organization of Materials</td>
<td>57.0</td>
<td>61.5</td>
<td>50.5</td>
<td>51.5</td>
</tr>
<tr>
<td>Metacognition Index</td>
<td>71.5</td>
<td>72.0</td>
<td>63.5</td>
<td>62.0</td>
</tr>
<tr>
<td>Global Executive Composite</td>
<td>69.5</td>
<td>69.5</td>
<td>65.5</td>
<td>63.0</td>
</tr>
</tbody>
</table>

*p < .05. The BRIEF-A utilizes T-scores to describe symptom severity, with higher scores indicating a greater level of symptom severity and clinical dysfunction

Correlation Between Depressive Symptoms and Performance

There was not a significant change in depressive symptoms from baseline to post-test (Z = -.831, p = .406). Spearman rank-order correlation coefficients did not identify significant correlations at baseline between depressive symptoms and cognitive performance. There were several correlations between baseline depressive symptoms and cognitive change across time that had noteworthy effect sizes; however, these findings were inconsistent, with several
measures showing improved performance with increased symptoms severity, such as Digit Span Backward ($r_s = .573$) and Digit Span Sequencing ($r_s = .475$), and other measures displaying decreased performance with increased symptom severity, such as Digit Span Forward ($r_s = -.389$) and Letter-Number Sequencing ($r_s = -.613$).

**Figure 1a.** Working Memory Index score at baseline and post-test for all participants
**Figure 1b.** Digit Span Total Raw scores at baseline and post-test for all participants

**Figure 1c.** Digit Span Backward scores at baseline and post-test for all participants
Discussion

This study is the first to examine a computerized online working memory intervention in a post-surgical adult epilepsy population. In terms of the acceptability of the treatment, 80% of the participants in the present study completed all or nearly all of the treatment sessions. These results compare favorably to the only other published study of an independently completed online working memory intervention in an adult neurologic population, in which only 9 (42.8%) of 21 participants with stroke finished 20 or more days of CogMed training in their homes (Westerberg, et al. 2007). There is a report that 100% of adults with acquired brain injury completed CogMed training within 21-25 days, although this study required them to complete the program in person at a rehabilitation facility (Lundqvist, et al. 2010). Our results also suggest a higher compliance rate than what has been found in previous studies assessing online treatment programs that target behavioral and emotional symptoms in adults with epilepsy; for
example compliance rates of 42.9% were reported for completion of all modules in a study of an online epilepsy self-management website (Dilorio, et al., 2009), and 30% compliance for completing all sessions of a web-based cognitive therapy for depression (Thompson, et al., 2010). As memory is a prevalent (Rausch and Babb, 1993) and disruptive (Hoppe, et al. 2007) cognitive deficit in patients with epilepsy, it is possible that our measured compliance rates reflect in part high patient motivation to participate in treatment. The level of acceptability of this treatment (as estimated from compliance) measured in the present study suggests that an online method of treatment delivery is suitable and feasible for the adult epilepsy population, which is particularly relevant given the transportation challenges that these patients often experience.

Although there was not a statistically significant group difference in compliance rates, both of those who completed less than 90% of training days were in the active condition. In light of this pattern, it is relevant to note that the active treatment condition required additional attention and vigilance in comparison to the control condition because of the titrated difficulty level, and only those in the active treatment condition were able to refer to their average and maximum scores during training. Therefore, there may have been differences across treatments that were not related to working memory capacity but, rather, were reflective of anxiety, frustration and fatigue, time on task or other motivational factors.

Due to the unexpectedly high compliance rate in our sample, there was not enough variability to assess whether a dose-dependent relationship existed between amount of training completed and objective or self-reported gains on neuropsychological measures. It is of note that both of the two participants who did not complete the program were in the active condition. It may be that the additional challenge level of the active program (which increased in difficulty as
patients improved on the tasks) would negatively impact overall compliance in a larger sample. One of the two participants with lower compliance (WM-001, 40% of days trained) still displayed improvement, discussed here as positive change scores on cognitive measures that were shown to have a statistically significant performance change by the group as a whole, despite not completing all assigned training days. Thus, it is possible to display positive change without completing all 25 training days.

The active treatment and control conditions had comparable cognitive abilities at baseline, meaning that the groups’ responses to condition were unlikely to reflect pre-existing differences. The results of treatment condition over time differed for the laboratory-based cognitive measures of attention and working memory, as opposed to the self-report measure of executive functioning on tasks in daily life (BRIEF-A).

For the laboratory-based measures, which are more similar to the trained tasks, there was no support for the primary hypothesis that the active treatment condition would improve over the course of the study more than the control condition. There was no effect of group assignment on any laboratory measure of cognitive ability that reached or approached statistical significance or a meaningful effect size.

When all participants were evaluated together, irrespective of treatment condition, they demonstrated statistically significant improvement between baseline and follow-up on certain laboratory tasks. Significant change over time was identified on the criterion task Digit Span Backwards and near-transfer task Digit Span Sequencing, but not on other criterion tasks and near-transfer tasks (Visual Span Backward or Digit Span Forward), or any of the far-transfer tasks (Letter-Number Sequencing or Arithmetic). To examine whether these increases in digit span scores were clinically meaningful, we turned to the maximal span lengths, rather than the
total raw scores described above. We found that the maximum number of digits recalled increased significantly only for the Digit Span Backward span, a criterion task, with 80% of participants displaying a maximum span increase of at least 1 digit. Although a single digit increase in span is not striking, it does represent a 22% increase over the baseline median of 4.5 items of information and may be large enough to impact everyday performance. Also, some participants increased their span by as much as 2 digits. This finding indicates that this type of computerized training could be useful in increasing working memory capacity for certain trained tasks in post-surgical patients with epilepsy.

The fact that the treatment groups did not differ as a whole from each other on the laboratory measures does not necessarily rule out the possibility that individual participants did derive benefit from the active treatment. We posited that those who did benefit would show consistent improvement across multiple measures. Therefore, for each individual, we also examined the percentage of the 5 criterion and near-transfer tasks on which he or she displayed positive change (operationalized liberally as a raw score at follow-up that was better than that at baseline by even a single point). The active condition participants showed positive change, with the six individuals showing increases on 40%, 40%, 60%, 60%, 80%, and 100% of trained tasks. In the control condition, participants showed gains on 20%, 40%, 60%, and 100% of trained tasks. Given that improvement on 50% of tasks would be expected by chance alone, scores exceeding that 50% were evident for 67% of active condition and 50% of control condition participants. Thus, only two individuals in the active treatment condition showed consistent improvement across tasks, similar to the one individual in the control condition.
No previous study of working memory interventions in adults with epilepsy has included a non-laboratory measure of executive functioning and working memory. Inspection of the BRIEF-A findings at baseline showed that virtually every participant with the exception of one reported clinically meaningful levels of working memory difficulty on everyday tasks (T-scores >65), and that working memory was disproportionately impaired in comparison to the other scales on the BRIEF-A. This result is consistent with a report from our lab with a sample of presurgical patients with TLE which also found that working memory was the most highly endorsed area of executive dysfunction in this population (Fischer, et al. 2015).

In contrast to the lack of significant group effects on the laboratory measures, the BRIEF-A results indicated that active condition participants reported significantly greater reductions in the severity of everyday problems associated with working memory difficulties than did those in the control condition. Although improvements in working memory function were reported, participants in both conditions still endorsed clinically significant working memory problems at post-test. This measure is derived from self-report, but it offers meaningful insight into working memory outcomes that are clinically relevant and not easily captured by laboratory measures. Other studies with the BRIEF in our laboratory and others have previously reported that scores on this measure are often at least partially independent of those captured by laboratory testing (Campiglia, et al. 2014; Fischer, et al. 2015).
Figure 2. BRIEF-A Working Memory subscale scores at baseline and post-test for all participants

Our findings are concordant with previous pediatric studies in children with low working memory capacity and children with intellectual disabilities that have displayed little difference on laboratory measures between the active treatment and active control conditions for CogMed programs (Dunning, et al 2013; Soderqvist, et al. 2012; Van der Molen, et al. 2010). These authors have suggested that, due to the level of deficits in those populations, even the low-grade control condition may have provided a sufficient challenge to participants to facilitate training and working memory gains. There are two lines of evidence suggesting that this explanation likely does not account for our findings. First, on the task for which our participants showed the lowest span length (Digit Span Backward), no participant had a span at baseline less than 4 items of information, meaning that everyone in the control condition was practicing throughout the training at a level well within their baseline ability. Second, the median Working Memory Index score was 97 at baseline, which is in the average range; therefore, our sample did not
demonstrate the extremely restricted ability levels described in the previous reports. Another potential explanation for the uniform improvement across conditions is that the control condition may not have been a true placebo condition but instead a lower gradation of the active training program that may have been effective in and of itself.

A recent study looking at a similar type of intervention (CogMed RM®) in a heterogeneous pediatric epilepsy sample found significant treatment effects for visual attention span, auditory working memory, and visual-verbal working memory (Kerr and Blackwell, 2015) when the active treatment condition was compared to a waiting list control condition. Specifically in relation to our study, they found statistically significant changes and sizable effect size in Digit Recall Backwards ($F = 25.93, p < 0.001, \text{Cohen’s } d = 0.95$), an analogous task to Digit Span Backward (Kerr and Blackwell, 2015). These results were interpreted as indicating that the intervention has the potential to facilitate development in criterion tasks in an epilepsy population.

Change in score between baseline and post-test may also reflect practice effects related to completing tasks twice within a 5-week interval. The WAIS-IV Technical and Interpretative Manual (Wechsler, 2008b) provides test-retest data for a sample of 298 individuals that can be used to evaluate practice effects in the present study. Those in the age band from 30-59 (which is closest to the ages of participants in the present study) displayed a slight increase in their mean working memory index scores between first testing ($M_{WMI} = 99.5, SD = 14.6$) and second testing ($M_{WMI} = 101.4, SD = 15.7$), with an average interval of 22 days between test and re-test (Wechsler, 2008b). Though some change in score is expected due to recent exposure to the test and practice effects, this would not seem to account for all of the change seen in working memory scores within our sample, which had a median change of 3 points on the WMI. With the
present study design, we are unable to rule out the possibility that a placebo effect contributed to the measured performance increases in both conditions.

Baseline depressive symptoms appeared to be correlated with change scores on several cognitive measures, but the nature of this relationship was inconsistent across tasks and greater reports of depressive symptoms were correlated with increases in certain working memory tasks but with deficits in others. Therefore, the present data do not provide evidence that level of depressive symptoms (which might have suppressed baseline cognitive measures) related in a meaningful way to the findings.

These results also have implications in terms of the mechanism by which working memory improvement occurs in response to treatment. Specifically, in light of results suggesting that working memory is partially dependent on the integrity of mesial temporal structures (Ranganath and Bluemenfeld, 2005; Wagner, et al. 2009), the present data represent the first evidence that it is possible to improve working memory in patients with unilateral temporal resections.

The low number of participants in this study severely limits the stability and the generalizability of the findings, as well as the statistical models that could be evaluated. The inclusion criteria for this study limited our potential participant pool in a single site study, and in conjunction with the need for daily internet access and the time commitment required to complete training, made it difficult to meet intended enrollment goals. Although the results do not support a superiority of the active treatment condition relative to the active control condition for laboratory tasks, they do provide evidence that active working memory practice may lead to significant self-reported improvements in performance in a cognitive domain that is particularly strongly affected in this patient population. It will be necessary to evaluate a larger sample, and
perhaps to add an inactive control condition, in order to better understand whether this intervention has clinical utility for a subset of those with epilepsy. Potential future research on this intervention in this population would occur in a multi-center format.

This study also suggests that this type of online working memory training intervention would be highly acceptable within the epilepsy population, with a high degree of treatment compliance. The obtained improvements in self-reported working memory performance, combined with the high degree of compliance for this program, implies that this treatment holds promise for improving the prevalent working memory difficulties that these patients display.
References


_Epilepsy Research and Treatment, 2011_, 1-11.