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Cognitive Rehabilitation of Prospective Memory Deficits after Acquired Brain Injury: Cognitive, Behavioral, and Physiological Measures

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COGNITIVE REHABILITATION OF PROSPECTIVE MEMORY DEFICITS AFTER ACQUIRED BRAIN INJURY: COGNITIVE, BEHAVIORAL, AND PHYSIOLOGICAL MEASURES

BY

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ABSTRACT

Acquired brain injury (ABI) affects approximately 3.5 million Americans each year and is associated with cognitive and emotional changes. Prospective memory (PM) deficits are important predictors of functioning in daily life for individuals with ABI. Previous studies have shown that cognitive rehabilitation therapy (CRT) via PM training has a high rate of success in improving quality of life, independence and productivity for ABI survivors. There is limited information on utilizing imaging techniques in relation to changes in cognition and behavior following rehabilitation; however, previous studies suggest that imaging provides evidence that CRT could be related to changes to underlying brain plasticity. The aim of this study was to evaluate what brain areas were activated during PM task stimuli in ABI individuals compared to healthy adults and measure the efficacy of a six-week tailored CRT design. Furthermore, a fMRI post-scan was used to determine if there were changes in the activation of cortical regions associated with the PM task following CRT compared to pre-therapy. 54 participants were enrolled in the study (35 individuals with ABI and 19 healthy adults). and given a neuropsychological battery and fMRI at baseline. Participants with ABI were randomized into two groups and received either six weeks of CRT individualized based on their pre-testing performance or brain education as control condition. Following treatment, the ABI participants received the same neuropsychological battery and a follow-up fMRI. Individuals with ABI performed significantly worse than healthy adults on all sub-scores of the Memory for Intention Screening Test (MIST), indicating significant impairment in PM function. There were no significant changes on the MIST in either the CRT group or the active control group following treatment. The results of this study suggest strong statistical evidence for sub-region activation in

frontal, cingulate, parietal, premotor, and temporal cortexes at baseline levels in ABI participants; however, there is no evidence of cortical changes post-therapy.

INTRODUCTION

Individuals with acquired brain injury (ABI) have reported prospective memory (PM) impairment to be the most prevalent type of memory problem (Mateer, Sohlberg, & Crinean, 1987) and the cognitive impairment that is most disruptive to daily life (Kinsella, Murtagh, Landry, & Homfray, 1996). These deficits interfere with independent living as many tasks, such as taking medication at the correct time, require intact PM functioning (Groot, Wilson, Evans, & Watson, 2002). Therefore, the development of rehabilitation strategies focused on the improvement of PM functioning is beneficial for individuals with ABI. The current study evaluated the efficacy of cognitive rehabilitation for PM functioning via cognitive, behavioral, and physiological measures. This was a controlled trial of cognitive rehabilitation using functional magnetic resonance imaging as a measure of physiological change.

Acquired Brain Injury

An ABI diagnosis is characterized as an injury that is non-hereditary, non-progressive, non-degenerative, and occurs after birth (Brain Injury Alliance of Connecticut, 2016). It is an umbrella term encompassing traumatic brain injury, stroke, aneurysm, brain tumor, vestibular dysfunction, and postsurgical complication that include but are not limited to anoxia or hypoxia (Ciuffreda & Kapoor, 2012). The leading etiology of ABI is traumatic brain injury (TBI) which is an injury or physiologic change in brain function due to an external force (Shum, Levine, & Chan, 2011). More specifically, TBI is associated with a direct impact to the brain resulting in the development of a contusion, hemorrhage, or axonal damage induced by accelerating or decelerating forces (Walker & Tesco, 2013). Approximately 1.7 million cases of TBI occur in

the United States every year resulting in over 5.3 million individuals living with a disability caused by a TBI in the US alone (Center for Disease Control and Prevention (CDC), Traumatic Brain Injury (TBI): Incidence and Distribution, 2004).

When the brain experiences trauma a variety of symptoms are evoked based on the location of damage. Widespread damage results from the initial swelling that creates further harm as the brain is encased in a hard shell, the skull, resulting in increased pressure (Mckee & Daneshvar, 2015). The higher order processing carried out in the different lobes is vulnerable to implications as they are closer in proximity to the skull (Ghajar, 2000). The frontal lobe is widely affected due to its large size and location at the front of the head. It is involved in numerous cognitive functions and damage can result in impaired executive function, judgement, and impulsivity (Novak & Bushnik, 2010). The temporal lobes are involved in verbal processing, memory acquisition, and hearing ability (Novak & Bushnik, 2010). Other sensations (motor, touch, visual, etc) are disrupted when damage is done to the parietal and occipital lobes (Novak & Bushnik, 2010). Localized damage results from focal lesions and diffuse axonal injury which occurs when nerve cells are torn from one another (Mckee & Daneshvar, 2015). Damage to the brain stem located at the base of the brain can result in arousal misregulation and implications in other regulatory function such as sleep and body homeostasis (Novak & Bushnik, 2010). Furthermore, difficulty monitoring attention, emotion, and short-term memory arise as the limbic system lies on the underside of the cerebrum (Novak & Bushnik, 2010). Overall, head trauma is highly variable and multifaceted with the possibility of implication in a variety of cognitive and psychical processes.

ABI reports as the leading cause of injury-related death and disability in the US affecting approximately 3.5 million Americans annually (Brain Injury Alliance of Connecticut, 2016),

making it a focal point for rehabilitation research. ABI can have significant effects on brain function creating deficits in areas of attention, learning, memory, and executive function (Raskin, 2010). These deficits can create implications in daily life affecting intellectual, physical, emotional, behavioral, and social abilities of the individual living with an ABI (Kinsella et al., 1996).

Prospective Memory

Prospective Memory (PM) is defined as the ability to remember to carry out a future task, also known as memory for intentions (Raskin, Buckheit, & Waxman, 2012). PM tasks are performed on a cue basis of either time or event. An example of this is remembering to take medication at an assigned time (time-based cue) or turn off the stove after use (event-based cue). PM is a multidimensional process that incorporates attention, working memory, retrospective memory, time perception, and metacognition (McDaniel & Einstein, 2001). Attention is required to form an intention and later recognize the cue for the intention (Scullin, McDaniel, Shelton, & Lee, 2010). Once an intention is formed, it is maintained in working-memory (McDaniel & Einstein, 2001). This translates to retrospective memory as one recalls the action needed to be formed at a given time (i.e. time-perception) (McDaniel & Einstein, 2001). Lastly, metacognition is the ability to evaluate whether the intention was executed correctly (Einstein & McDaniel, 2005).

PM is categorized into two task-based types: event-based and time-based (Kliegel, Martin, McDaniel, & Einstein, 2010). An event-based task is externally cued requiring outside assistance such as handing someone an envelope to cue a response of addressing the envelope (Raskin et al., 2012). Whereas, a time-based task is self-cued and requires the individual to keep track of the time. Once a given waiting period is complete, they then need to remember to

conduct the intended action. An example of this would be checking the clock at 3:25 pm with the instruction "in 2 minutes write your name on your paper" then the individual would need to self-monitor and at 3:27 pm write their name on their paper (Raskin et al., 2012). On average, individuals with ABI perform significantly worse on time-based tasks compared to event-based task (Kliegel et al., 2010). However, they perform significantly worse in both categories when compared to healthy adults (Shum, Valentine, & Cutmore, 1999). These deficits are demonstrated using neuropsychological measures of PM and are used to design specific rehabilitation models to overcome impairment. Furthermore, cognitive rehabilitation therapy via PM training has proven to have a high rate of success enhancing quality of life and independence (Raskin, S. & Sohlberg, M, 2009).

Cognitive Rehabilitation

Rehabilitation Approaches

Cognitive rehabilitation is a form of therapy that attempts to restore impaired cognitive function for individuals with ABI and improve daily functioning (Gordon & Hibbard, 1991). Cognitive Rehabilitation Therapy (CRT) is broken down into three standard approaches: compensatory, restorative, and metacognitive (Sohlberg, 2006; Kennedy, Coelho, Turkstra…Khan, 2007).

A compensatory, or behavioral, intervention would be teaching an individual to use devices or strategies to aid in the completion of planned task (Wilson, Emslie, Quirk, & Evans, 2001). For example, the use of an external aid to compensate for deficits would be the use of a notebook or electronic aids for assisted memory function (Sohlberg, 2006). This approach uses external modifications and cues to compensate for memory impairment; however, it does not improve the underlying PM deficits, it simply compensates to reduce their effect in daily life.

A restorative approach, in contrast, involves direct intervention aimed to improve or restore the lost cognitive function (i.e. attention processing training) (Raskin & Mateer, 1999). This approach is supported by theories of neuroplasticity which state that the brain is capable of substantial structural and functional reorganization after injury (Sophie Su, Veeravagu, & Grant, 2016). Rote repetition exercises have been shown to have considerable impact on memory improvement post injury (Raskin, 2010). Attention processing training (APT) is another strategy used to target many facets of attention (selective, divided, sustained, and alternating) based on demonstrated deficit in individuals with ABI (Sohlberg, McLaughlin, Pavese, Heidrich, & Posner, 2000). It is a hierarchical program that has previously shown progressive improvement in areas of attention, working memory, and performance speed (Palmese & Raskin, 2000).

Lastly, a metacognitive approach uses a self-monitoring and awareness strategy to facilitate completion of a task (Sohlberg, 2006). Visual imagery training is a common metacognitive approach in which individuals visualize themselves completing a task that they must perform (intention) in the future. This is implemented to increase awareness and planning of the intention that must be carried out in the future (Raskin, Smith, Mills, Pedro, & Zamroziewicz, 2017).

Most CRT use a combination of all three approaches to successfully generalize treatment to daily life. The goal of generalization is to (1) consistently show gains from rehabilitation with the same material and setting on numerous occasions, (2) improvement is shown on similar sets of tasks, and (3) functions gained in task training are translating to daily life functioning (Gordon, 1987). With the information obtained through neuropsychological assessment and modules set in place, CRT can be individualized for each ABI individual.

Treatment Modules

There are five individual treatment modules targeting areas of cognitive deficit related to prospective memory in this current study: attention, encoding the cue, retrieving the intention, awareness and evaluation of outcome, and time perception. For primary deficits in attention, attention process training (APT-3) and increasing cognitive load is used. APT-3 is a computerized attention training program aimed to improve underlying attention deficits resulting from acquired brain injury (Sohlberg et al, 2000). The comprehensive program can be manipulated to accommodate mild to severe impairment in areas of sustained attention, working memory, selective attention, suppression, and alternating attention (Sohlberg & Mateer, 2010). Additionally, the program incorporates the metacognitive strategy of self-monitoring at the end of each task completion to allow for awareness and motivation (Sohlberg & Mateer, 2010). In the increasing cognitive load module participants are asked to remember an increasing number of tasks that should be carried out at various times that gradually overlap (Raskin, 2016).

The module used for deficits in encoding the cue is decreasing cue focality and decreasing cue-intention relatedness. Decreasing cue focality is a thirty-minute exercise in which twenty cues that decrease focally (i.e. become less related to the ongoing activity) are asked to be completed at an increasing amount of time after three consecutive successful completions (Raskin 2016). An example would entail an individual to conduct an ongoing task such as a word search. During this task an intention such as remembering to circle the title of the word search after 2 minutes would have a high focality whereas a later task such as telling the administrator what you had for breakfast after 4 minutes would have a low focality as it has no relation to the ongoing task. Decreasing cue-intention relatedness is a thirty-minute exercise that consists of ten cues and commands in which the relatedness of the cues decrease while the time inconsistency

increases (Raskin, 2016).

Visualization training and enactment are the modules used for targeting deficits in retrieval of intention. Visualization training is an internal strategy in which the individual pictures themselves carrying out an instructed intention when the task was initially assigned providing a visual representation of the future intention that must be retrieved (Malia et al., 2004). Enactment is another internal strategy in which the individuals acts out the intention when the task was first administered to create a repetitive motion that helps retrieve the intention after a delayed period of time (Raskin, 2016).

For deficits in awareness/evaluation of outcome, goal management training is the module used for rehabilitation. Goal management training (GMT) is an executive functioning intervention strategy that targets goal processing and sustained attention (Levine, Robertson,… Stuss, 2000). GMT is an interactive program that promotes improvement in organization and completion of complex real-life tasks that are challenging for individuals with executive functioning deficits. The main goal is to periodically stop an ongoing task to monitor and adjust goals to ultimately reach completion (Stamenova & Levine, 2018).

Lastly for demonstrated deficits in time perception, time perception training is used in the cognitive rehabilitation program. Time perception training is a rote repetition module in which the individual is asked to carry out tasks at specific times. There is a clock and timer available so that the individual could use their judgment to complete the right task at the appropriate time (Raskin, 2016). Overall, a combination of specific treatment modules is catered to the ABI individual based on the results from neuropsychogical assessment outcomes.

Rehablitation Strategies

There have been multiple approaches to cognitive rehabilitation in PM performance for

individuals with ABI in scientific literature. There is no empirical evidence that there is a time sensitivity on treatment (Gordon & Hibbard, 2005); however, recent studies suggest intervention at later stages post-injury may be more beneficial (Kennedy & Turkstra, 2006). In regard to intervention strategies, it is demonstrated that memory training programs and compensatory strategies are an effective method of improving cognitive deficits (Piras, Borella, Incoccia, & Carlesimo, 2011). Previous ABI rehabilitation has focused on attention (Sohlberg et al, 2000), memory (Sohlberg, White, Evans, & Mateer, 1992), executive function (Levine et al, 2000), comprehensive-holistic treatment (Cicerone, Dahlberg,…Catanese, 2005), and technology based intervention (LoPresti, Mihailidis, & Kirsch, 2004). Evidence supports ABI cognitive rehabilitation is successful with a combination of these various intervention approaches (Tsaousides & Gordon, 2009); therefore, the current study takes aspects from each category to design a cognitive rehabilitation treatment program that is multifaceted and can be catered to individual participant deficits.

Timeframe and structural design for the study was based on previous studies. Fleming et al. (2017) demonstrated that a six-session program was an effective design for improving PM performance via compensatory and metacognitive approaches. This once a week intervention program allows for a manageable time commitment and participant retention. Furthermore, Shum et al. (2011) conducted a similar study with a randomized control trial that included an active control condition. This condition aimed to have a comparable level of participant-therapist interaction while being unrelated to the self-awareness and PM training being conducted in the rehabilitation group. Results from these studies aided in the double-blind, randomized control trial design of our 10-week, 6 session, cognitive rehabilitation study.

Based on the fact that ABI individuals make up a heterogenous population, due to

severity and localization of cerebral damage, makes it difficult to standardize cognitive rehabilitation therapies (Poylishock & Katz, 2005). Neuroimaging is a tool that uses structural and functional measures to aid in the identification of injury. Structural images indicate regions of damage while functional measures demonstrate performance in correlation to cognitive tasks (Ricker, DeLuca, & Frey, 2016). Functional imaging, such as functional magnetic resonance imaging (fMRI), measure and monitors cerebral activity and consequences of plasticity associated with injury (Strangman, O'Neil-Pirozzi,…Glenn, 2005). This provides information on the effectiveness of rehabilitation and can help efficiently customize rehabilitation design to adapt to each individual brain injury.

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is a noninvasive neuroimaging technique for measuring and mapping neural activity via blood flow (Smith, Beckmann,…Glasser, 2013). This technique detects the blood-oxygen-level-dependent (BOLD) signals that have high spatial resolution making them desirable for locating specific brain networks associated with cognitive functions (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). There have been studies conducted that demonstrate a relationship between PM deficits and damage to prefrontal cortex; however, this was based on neuropsychological testing assumptions about underlying brain regions (Umeda, Kurosaki, Terasawa, & Miyahara, 2011). There is a lack of evidence when looking at brain regions associated with PM via neuroimaging in adults with ABI. Gordon, Shelton, Bugg, McDaniel, & Head (2011) looked at grey matter volume in healthy adults (HAs) and very mildly demented older adults undergoing PM tasks; however, the degree of cognitive deficit was not significant between the two groups and the data represented that of associated brain regions for a HA. Therefore, designing a study that compares healthy adult BOLD signals

to the results of individuals with ABI while performing a PM task may help to explain PM deficits and mechanisms of recovery.

In healthy adults, studies using neuroimaging have shown frontal lobe activation as a critical brain region involved in PM (Simons, Scholvinck, Gilbert, Firth, & Burgress, 2006). The brain region that appears to be involved in formation and maintenance of intentions are rostral prefrontal cortex (Brodmann Area 10), ventrolateral prefrontal cortex, lateral parietal cortex, and anterior cingulate (Burgress, Gonen-Yaacovi, & Volle, 2011). Brodmann Area 10 (BA10) has been shown to have activation related to cue identification and intention retrieval during ongoing tasks; whereas the lateral locations of the PFC tend to correlate with aspects of delayed intentions (Burgress et al, 2011). In the parietal lobe, Brodmann Area (BA) 40, the precuneus (BA 70), and the anterior cingulate (BA 32) are also activated during PM paradigms (Burgress et al., 2011). However, there is not data on PM functioning in ABI individuals; therefore, further investigation is required.

Additionally, there is evidence on the use of fMRI to measure cognitive rehabilitation outcomes; however, evidence is lacking in regarding to PM measures. fMRI is an applicable measure of physiological functioning post-ABI due to its noninvasive procedure that is readily available in clinical settings, though it has posed difficulties regarding signal detection, brain activation measurements, movement, and artifact (Hillary et al. 2002). However, when applied to cognitive rehabilitation outcomes it has afforded researches the opportunity to examine changes at the cerebral level that coincide with behavioral changes (Hillary et al., 2002). Research on rehabilitation strategies ranging in focus (sensorial modifications, attention, behavior, etc) have all demonstrated that rehabilitation is beneficial in the reduction of physiological disturbance such as reduced cortical signal to noise, disruption of oscillatory rhythm, and increased

performance variability (Galetto & Sacco, 2017). Additional outcomes of neuroimaging studies have highlighted how cognitive rehabilitation can significantly modify cerebral activation (Kim et al., 2009; Chiaravalloti, Dobryakova, Wylie, & DeLuca, 2015). Kim et al. (2009) used fMRI with a visuospatial task to assess physiological changes associated with cognitive rehabilitation. Prior to rehabilitation fMRI analysis showed increased activation in the frontal and temporoparietal lobes and decreased activation in the anterior cingulated gyrus, SMA, and temporooccipital regions in ABI participants compared to healthy adults (Kim et al., 2009). Results showed that after cognitive rehabilitation performance of attention tasks improved and changes in the attention network activation (frontal lobe decrease and anterior cingulate cortices as well as precuneus increase) were found (Kim et al., 2009).

The current study is designed to use neuroimaging to assess the physiological correlates of PM performance in individuals with ABI and determine if PM tasks are activating the same location in ABI survivors compared to healthy adults and to determine any changes in this activation following treatment. A randomized controlled double-blind design was used to investigate the brain processing and PM performance in ABI individuals before and after undergoing cognitive rehabilitation.

Hypotheses

1. We hypothesize that at baseline individuals with ABI will score significantly lower than HA individuals on standardized measure of PM as well as on the assessments of memory, attention, and executive functions and on measures of generalization and quality of life
2. We hypothesize that individuals with ABI will show significantly greater improvement on a standardized neuropsychological battery in the cognitive rehabilitation therapy

condition (CRT) compared to the non-therapy attention control condition (AC)

3. At baseline, we predict ABI participants will have reduced activation in regions-of-interest that previously have been linked to PM compared to healthy participants
4. We predict that brain activation in dorsomedial frontal gyrus, anterior cingulate, and bilateral putamen regions-of-interest will increase relative to pre-therapy baseline levels for ABI participants in CRT and brain activation in ventromedial frontal gyrus will decrease compared to the AC

METHODS

Participants

Participants were recruited through contact to the Brain Injury Alliance of Connecticut, local support groups, and patients of study-affiliated physicians. Eligibility for participation for ABI participants required the individual to be between the age of 20 and 65, a minimum of one-year post-injury, right-handed, and have obtained a moderate to severe brain injury classification (GCS<12) that was determined based on a review of medical records. Eligibility for healthy adult participants required the individual to be between the age of 20 and 65 and right-handed. Additionally, healthy adult participants were recruited to reflect similar age and education measures to that of participants with an ABI. Further exclusion criteria for both ABI and healthy adult participants included non-English speaking, previous neurological or psychiatric illness, diagnosed learning disability, severe anxiety or depression, dementia, illiteracy, or significant hearing or visual impairment.

Following these guidelines, 85 ABI participants were recruited and screened for this study; 16 were ruled out due to exclusion criteria and 15 were unresponsive or not interested. Of the 54 individuals consented and enrolled into the study, 10 withdrew at some point during the

six weeks of cognitive rehabilitation. Pretesting and pre-fMRI data was analyzed for all 54 individuals consented. However, post treatment comparison was only conducted on the 44 individuals that successfully completed the study, experimental group of 25 adult individuals that have obtained an ABI and 19 adult individuals in the healthy adult condition. Of the 25 original ABI participants enrolled in the experimental condition, 10 were unable to participate in the fMRI portion of the study due to implanted metal in the body. These individuals participated strictly in the neuropsychological portion of the study. The 15 remaining individuals who passed the fMRI screening test partook in both the fMRI portion and neuropsychological testing portion of the study.

Medical records were obtained for all ABI participants enrolled and each ABI participate had a baseline PM performance of less than 10 minutes. With these severely low PM performance reports and a verification based on medical records it was concluded that all ABI participants range in diagnosis from moderate to severe ABI. Table 1 indicates ABI participant demographic and disease characters.

Table 1. *Participant Demographic and Disease Characteristics mean and (standard deviation)*

Characteristics	CRT (n = 18)	AC (n=7)	HA (n=19)	*p*
Age (y)	45.7 (11.5)	46.6 (11.1)	29.2 (7.4)	< 0.0001
Education (y)	15.7 (3.0)	16.3 (2.9)	16.0 (2.7)	1.000
Sex	F=10 M=8	F=4 M=3	F=11 M=8	—
Etiology of Injury	3 ABI, 10 TBI, 1 STR, 3 T, 1 BA	5 TBI, 1 STR, 1 BA	—	—

[1]In Years [2]ABI=Acquired Brain Injury, TBI=Traumatic Brain Injury, STR=Stroke, BA=Brain Aneurysm, T=Tumor

Materials

Neuropsychological Testing

Table 2 depicts a battery of neuropsychological measures that were administered focused on the cognitive areas of executive functioning, attention and memory. The primary measure of interest was prospective memory.

Table 2. *Neuropsychological Battery*

Treatment Module Category	**Evaluation**
Executive Function	Animal Naming
	Controlled Oral Word Association
	Stroop Color and Word Test
Attention	Brief Test of Attention
	Digit Span
Prospective Memory	Memory for Intention Screening Test (MIST)
Retrospective Memory	Brief Visuospatial Memory Test (BVMT-R)
	Hopkins Verbal Learning Test (HVLT-R)
Mood/Personality	Beck Anxiety Inventory (BAI)
	Beck Depression Inventory (BDI)
Generalization	Comprehensive Assessment of Prospective Memory (CAPM)
	WHO-QOL-BREF

Assessment of Executive Function

Executive Function was assessed using the Animal Naming Test of the Boston Diagnostic Aphasia Exam (Goodglass, Kaplan, & Barresi, 2001), Controlled Oral Word Association Test (Patterson, 2011), and Stroop Color and Word Test (Sapina & Tagini, 2017). The Animal Naming test is used to measure category fluency (Shao, Janse, Visser, & Meyer, 2014). Participants are asked to recite as many animals of any kind as they could think of for a total of sixty seconds. The total score was the number of animals minus errors of repetition, or errors of non-animals. Similar to Animal Naming, the Controlled Oral Word Association Test is

a measure of phonemic fluency (Patterson, 2011). The test is broken down into three letter categories: F, A, and S. Participants were given sixty seconds for each letter category to recite as many words beginning with that letter as possible. Proper nouns and the same word with different endings were excluded from the total. Lastly, the Stroop Color and Word Test was a measure of selective attention and cognitive flexibility. It was a three-page test consisting of word, color, and word-color lists. The word page was a list of randomly repeated color names (red, green, and blue) printed in black ink. The color page was a list of XXX printed in the colors red, green, or blue in random order. The color-word page was the words red, green, and blue printed in the colors red, green, or blue. Participants read the list of words, said the color the XXX's were written in, and said the color of the word "red" was written in (i.e. blue) as rapidly as possible. Time for each trial was recorded (Scapina & Tagini, 2017).

Assessment of Attention

Two neuropsychological measures were used to test attention: Brief Test of Attention (BTA) and Digit Span. The BTA is a short test of auditory selective attention broken down into two conditions with 10 trials each (Schretlen, Bobholz, & Brandt, 1996). A tape recorder was used for administration that recites a series of numbers and letters. For the first condition, the examinee was asked to report how many numbers were present in each data set. For the second condition, the same data sets of numbers and letters were announced, and the examinee was asked to report how many letters they heard in each data set. Over the course of the 10 trials the data sets increased from 4 to 18 number and letter combinations. Each trial was worth 1 point and the test was scored up to 20 points. The Digit Span is an assessment of working memory and attention. Conducted verbally, the Digit Span is a sequence of numbers that the participant repeated back to the administrator. Three separate trials were administered and the participant

either repeated the numbers aloud in the same order as they were given, reverse order, and ascending order. This process was continued until the participant commits two consecutive errors. Each set of digits correctly repeated was worth a single point and was totaled for scoring (Blackburn & Benton, 1957).

Assessment of Memory

The Memory for Intentions Screening Test (MIST) (Raskin, 2009) was the primary outcome measure for prospective memory. The test was designed to take approximately 30 minutes, containing 8-trials on top of which participants engage in an ongoing task, a word search puzzle. Summary score, time-based scales, and event-based scales were the primary area of examination for this test. There were four measure of time- and event-based tasks each that consist of either a 2- minute or 15-minute delay interval and either a verbal or action response modality. Score was 0-2 based on correct response at the correct time (2), correct response at the wrong time (1), wrong response at the correct time (1), or wrong response at the wrong time / omission (0). The MIST allowed for separate scoring of time-based trials, event-based trials, 2-minute time delay periods, 15-minute time delay periods, verbal response trials, and action response trials. Each scoring group had an 8-possible point value adding to a total score of 48 possible points. This did involve inclusion of the score of each trial three times in the total score (e.g. Trial 1 was a verbal response to a 2-minute delay time-based cue). A digital clock was constantly present for time reference and the ongoing task was non-focal as the word search was not related to the prospective memory items. Following the 8 PM trials, participants were asked 8 recognition questions regarding the PM tasks completed. The recognition scale was included to determine whether PM failures were encoding versus retrieval failures. Impairment on recognition items was likely a deficit in retrospective memory rather than prospective memory.

The Brief Visuospatial Memory Test-Revised (BVMT-R) and the Hopkins Verbal Learning Test (HVLT-R) were measures of retrospective memory. In addition, the BVMT-R was a good tool for measuring visuospatial learning and memory abilities across clinical settings (Benedict, Schretlen, Groninger, Dobraski, & Shpritz, 1996). The BVMT-R consists of three learning trials in which the participant looks at page with six figures on it for 10 seconds. After the viewing period was completed, the participant was instructed to draw each figure in the correct orientation and location in a separate response booklet. After a 25-minute delay period, in which other unrelated tasks are occurring, the participant was asked to again draw the same figure in the correct orientation and location on the delayed recall page of their booklet. After the delayed recall, there was a series of recognition questions in with the participant was presented with 12 figures and was asked to response yes or no to if the figure was in the original set (Benedict et al., 1996).

The HVLT-R was used for assessment of verbal learning and memory ability. This test included a list of 12 nouns (four words drawn from three semantic categories) that was read aloud to the participant. The goal of the test was for the examinee to repeat as many words as they can recall from the list of 12 nouns in any order. The process was repeated two more time consecutively and then after a 20-25 minute delay period the examinee was asked once more to recall as many words from the original list of 12 nouns. After the delay recall task, the participant was presented with a longer list of 24 nouns, the 12 original words, 6 from the three semantic categories but not on the original list, and 6 nouns with no relation to the original list (Belkonen, 2011). These tests were selected due to their effective representation of memory and because they have alternate forms that can be administered during pre- and post-testing.

Assessment of Mood/Personality

The Beck Anxiety Inventory (BAI) and the Beck Depression Inventory (BDI) (Beck & Steer, 1993; Beck, Steer, & Garbin, 1988) were used as measures of current mood and personality of the individual. The BAI is a 21-item, self-report rating inventory that assess the anxiety level of an individual and is seen in research including treatment-outcome studies for individuals who have experienced trauma (Steer & Beck, 1997). The BDI is a 21-item, self-report rating inventory that measures characteristics of depression (Beck, Steer, & Garbin, 1988). Both measures were used to assess anxiety and depression as an exclusion criterion of the participant.

Generalization Measures

Section A: Frequency of Forgetting of the Comprehensive Assessment of Prospective Memory (CAPM) was used as a self-report generalization measure of PM. The CAPM is a questionnaire that evaluates the frequency of PM failures with brain injury (Chau, Lee, Fleming, Roche, & Shum, 2007). It provides a measure of an individual's self-awareness on PM dysfunction in basic activities of daily living (BADL) and instrumental activities of daily living (IADL) (Mioni, McClintock, & Stablum, 2014).

The World Health Organization Quality of Life abbreviated scale (WHOQOL-BREF) was used as a generalizable measure of how the impact of injury and impairment on daily activities and behavior was perceived by the individual (The WHOQOL Group, 1994a). The WHOQOL-BREF consisted of 26 comprehensive questions covering four domains: physical health, psychological, social relationships, and environment (The WHOQOL Group, 1994b). It was used to assess the patient's overall well-being and provide a measure to support a holistic approach to treatment.

Functional Magnetic Resonance Imaging

Stimulus Delivery/Response Recording

E-Prime (Psychology Software Tools, Inc.) was used to implement fMRI prospective memory task. The stimulus was projected via a screen behind the participant's head in the MRI and participants viewed this screen using a mirror on the head coil. An MR-compatible 5-button fiber optic response device (Current Designs, Inc.) was used to acquire behavioral responses. Each fMRI task was programmed to track accuracy and reaction time for conditions of interest for offline analysis. Participants were able to communicate with staff via an auditory sound system delivered by 30 dB sound-attenuating headphones while in the MRI machine.

MRI Sequences

fMRI gradient EPI (TR/TE 720/36 msec, flip 52°, multi-band AF=8). Fieldmaps (TR/TE 780/5.19, flip 50°, AF=1, 3:10 min; and TR/TE 7600/67 msec, flip 80°, AF=1, 0:23 min, run twice with reversed R>>L phase encoding) (EPI/fieldmap sequences have 2.1 mm isotropic voxels, 64 interleaved slices, 210 mm FOV). T1-weighted (3D MPRAGE, TR/TE/TI=2400/2.07/1000 msec, flip 8°, FOV=256×256mm, 0.8 mm isotropic vox; 7:02 min). T2-weighted (TR/TE=3200/565, FOV=256x256, 0.8 mm isotropic vox; 6:45 min). Structural images were Radiologist-assessed to be free of macroscopic pathology. Daily MR stability and question and answer measurements will ensure scans are of equal quality throughout the entire project.

Head Motion

Data was examined via online QA within 3 minutes. EPI data with movement >1 voxel (2 mm) was replaced using parallel task versions. As shown to be most effective in our recent methods comparison (Damaraju, Allen,…Calhoun, 2014) minor motion will be mitigated via

AFNI 3dDespike and with motion parameter regressor and time point censoring (frame wise displacement >0.5 mm (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012) during (FSL) or prior to subject wise modeling (ICA).

PM Task

The fMRI task was an event-related PM task in which participants were required to classify capital letters based on perceptual features (ongoing task) or preform an alternative task cued by infrequent stimuli (PM task). The specific perceptual features task was to determine if the presented letter consisted of all straight lines (e.g. A or N) or contained curved lines (e.g. D or O). This served as the ongoing task. During this ongoing task, PM targets were presented in a three-letter word form (e.g. CUP) which served as a cue for the participants to neither classify as straight nor curved but to pick a third classification if any of those three letters was later presented.

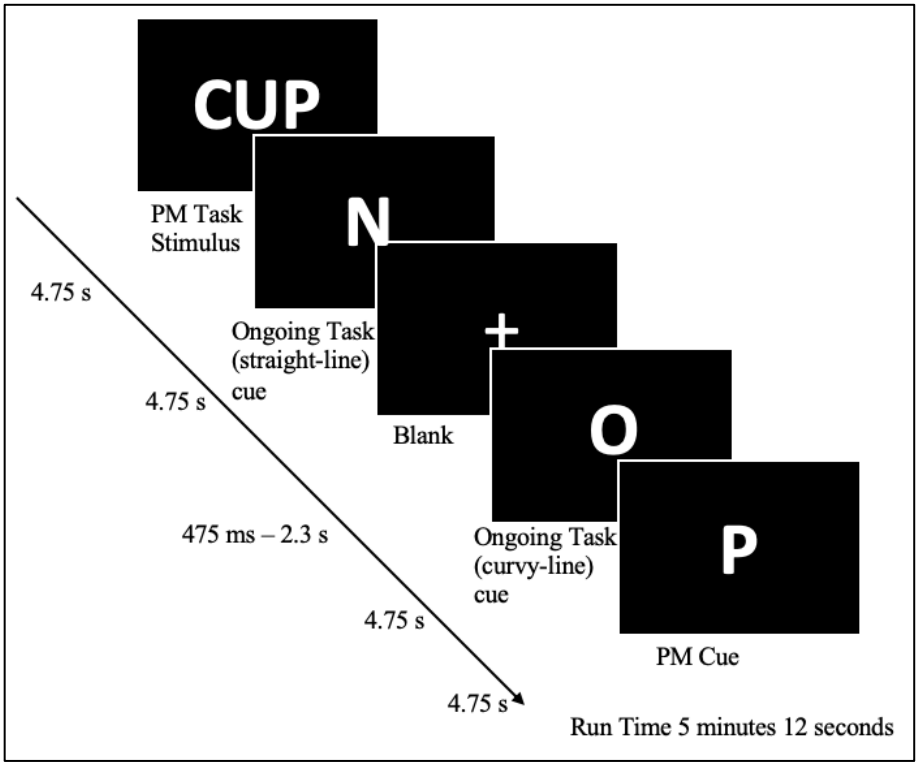

Figure 1. fMRI design for PM task

The program was designed to have six runs (3 set combinations); at the beginning of each run a three-letter word stimuli was presented. Each of the 6 runs consisted of 26 straight, 26 curved, and 8 PM stimuli. Each stimulus was presented for 4.75 seconds. There were blank screens intermixed that varied length from 475ms to 2.3 seconds to avoid predictability and habituation. Therefore, the total time for each run was approximately 5 minutes and 12 seconds, resulting in a scan time of 32 minutes. The randomized design allowed for an appropriate gap between PM task letter presentation to allow for delayed intention. This unpredictable sequence served to minimize learning and awareness of underlying rules and objectives. Participant response was recorded on a response pad correlating to the index, middle, and ring fingers on their right hand. The index finger (left key press) indicated a straight letter response, the ring finger (right key press) indicated a curved letter response, and the middle finger indicated a PM task stimuli response. Performance accuracy and reaction time were recorded for post-hoc analysis.

Procedure

This study was designed to take place over a 10-week period in which participants underwent fMRI and/or neuropsychological testing before and after a 6-week treatment period (1-hr session each week). The treatment period included either cognitive rehabilitation therapy or brain education (attention control condition). The design was set in place to allow for any changes that might be due to cortical reorganization which was modeled after motor and sensory plasticity studies (Raskin & Sohlberg, 2009). Therapy sessions were individually designed for each ABI participant based on their scores on the MIST and neuropsychological assessments (Table 2).

Therapy exercises included prospective memory training (PMT), attention processing training (APT-III), goal management training (GMT), and visualization modules. PMT cognitive intervention training required an individual to remember a task over an allotted time span starting at two-minutes while conducting an ongoing task. If the individual correctly remembered the task after the time delay for five consecutive tasks then the time increment increased by one minute (Waldum et al., 2016). APT-III exercises were designed to target different components of attention (basic sustained tasks, executive control selective attention tasks, working memory tasks, executive suppression tasks, and alternating tasks) and were administered in a computerized form (Sohlberg & Mateer, 2010). GMT was used as a metacognitive intervention for executive dysfunction in which computerized tasks were administered and required the individual to periodically state their goals before and during task execution (Krasny-Pacini, Murtagh, Landry, & Homfray, 2013).

If a participant was randomly selected for the attention control condition (AC) they underwent six, one-hour sessions of brain education equivalent to the time commitment for cognitive rehabilitation. The brain education condition consisted of video and slideshow presentation of neuroanatomy, neurophysiology, neurochemistry, and brain injury. Each presentation had a quiz component with questions throughout the task as well as a comprehensive quiz at the completion of the presentation. Additionally, participants were asked to read and engage with a TBI information comic series addressing headaches, emotional changes, sleep, concussions, and over around understanding TBI (Novack & Bushnik, 2002). Table 3 depicts a general breakdown of the techniques used during the six-week intervention period.

Table 3. Overview of CRT and AC techniques

Compensatory Strategies (completed in CRT)	
Description	Aim
Use of memory aids (E.g. diary, electronic device, calendar)	To aid in familiarizing participants with a device that is comfortable for them to use during everyday activities
PM education	To develop an understanding of what PM is and how it is affected by TBI
Family/friend training	To involve participant's significant other or caregiver to help encourage memory aid use outside of the clinical environment
Restorative Strategies (completed in CRT)	
Description	Aim
APT	To improve ability in attention, executive function, and working memory
PMT	To improve ability in prospective memory through route repetition
Metacognitive Strategies (completed in CRT)	
Description	Aim
Self-reflection activities (E.g. GMT, PM performance self-prediction measures and self-evaluation)	To encourage self-monitoring and for participants to gain insight on how they correct self-error
Performance Feedback (E.g. verbal, written, or computerized)	To give the participant opportunities to gain insight on their performance and create strategies for future tasks
Brain Education (completed in AC)	
Description	Aim
PM education	To develop an understanding of what PM is and how it is affected by TBI
TBI education	To provide information on the cause, symptoms, and long-term side effects (E.g. issues with sleep, emotional regulation, headaches, etc)
General brain education (E.g. anatomy, physiology, chemistry)	To provide information about the brain and the repercussion of injury to specific location

Individuals eligible for the fMRI portion of the study were administered the fMRI task, neuropsychological tests, the MIST, and generalization measures at the beginning of the study. Individuals that participated only in the neuropsychological portion of the study were administered neuropsychological tests, the MIST, and generalization measures at the beginning of the study. After the initial testing period, the ABI experimental group was randomized into

two categories: Cognitive Rehabilitation Therapy (CRT) (n =18) or Attention Control Condition (AC) (n =7), using a random number generator. This determined which participant would undergo individualized cognitive rehabilitation and which would receive standardized brain education. Immediately following the 6-week treatment period, each form of testing, fMRI task, neuropsychological tests, the MIST, and generalization measures, were re-administered. Healthy adults only underwent the initial two-week testing period in which they were administered the fMRI task, neuropsychogical tests, the MIST, and the generalization measures. All testing was administered by a research assistant trained in testing administration by standard procedure and blind to the randomized treatment condition assigned to the participant.

Statistical Analysis

All 54 participants enrolled in the study were used for baseline data analysis. Only participants that completed all ten weeks of the study were included in the performance data analysis (n = 44). The CRT and AC groups were compared on all demographic variables (age, sex, years of education, months post injury, and etiology of injury). IBM SPSS and Microsoft Excel were used to analyze all participant data. Baseline PM function, neuropsychological testing and generalization measures were all compared using analysis of variance (one factor ANOVAs) with Fischer's LSD for multiple comparison between healthy adults, the active control condition and the cognitive rehabilitation condition. These measures were also compared pre- and post- treatment in the ABI participants in the CRT and AC by means of a paired-sample t-test.

The Human Connectome Project pre-processing pipelines (Glasser, Sotiropoulos, … Jenkinson, 2013) were used for structural image-guided brain atlas normalization for the fMRI sequences. The image modalities use T1-weighted and T2-weighted structural scans to represent

the resting-state and task-based functional MRI scans. FreeSurfer was used for segmenting subcortical grey matter, skull-stripping, and parcel smoothing on 1 mm down sampled T1w/T2w data to analyze structural volumes (Fischl, Salat,…Dale, 2002). FSL FLIRT+nonlinear FNIRT algorithms were used for T1w/T2w image atlas analysis (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). fMRI data was de-spiked and motion controlled (Mazaika, Whitfield, & Cooper, 2005) and underwent the same distortion correction as the T1w/T2w data. All data was resampled to atlas space, normalized, and smoothed in preparation for analysis. Task activation to each experimental condition was evaluated using FSL FEAT with FMRIB Improved Linear Model (FILM), using geodesic Gaussian algorithms to estimate autocorrelation. A double- gamma HRF convolution was used to translate event onset of explanatory variables (PM, straight and curvy conditions) into regressor that were fit to BOLD time series. FSL's FLAME random-effects models were used to confirm activation and compare group profiles. One-sample t-tests were conducted to assess task activation in localized peak activation within predicted regions-of- interest.

RESULTS

Performance on clinical measure of PM

There was significant difference ($p < .05$) between healthy adults (HA) and individuals with acquired brain injury (ABI) on total baseline performance on the summary score of the MIST (Figure 2) and all additional sub-section measures (Table 4). There are no significant differences on any of the sub-scores between the two ABI conditions (CRT and AC); however, Fischer's LSD analysis revealed that the HA and AC groups did not show significant differences on the event-based and 2-minute delay ($p >.05$), indicating that the performance of ABI individuals in the AC was between that of the individuals in the CRT and HA groups. There

were no significant changes on the summary score (Figure 3) or any of the sub-scores in either the CRT or AC group following six weeks of treatment (Table 5). Overall, ABI individuals performed significantly worse on all sub-section measures of the MIST demonstrating significant impairments in PM function.

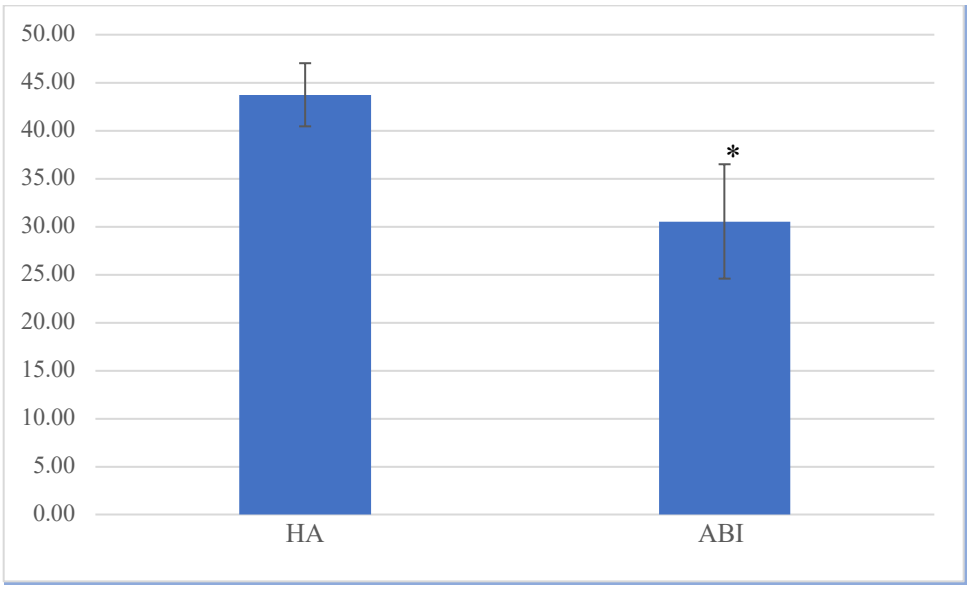

Figure 2. *HA and ABI baseline performances on summary score of the MIST*
*Indicates significantly lower performance of ABI compared to HA

Table 4. *Healthy adults vs. ABI group performance on MIST sub-sections prior to treatment*

	HA (n=19)		ABI (n=37)			
	Mean	**SD**	**Mean**	**SD**	**F**	**Cohen's d**
2-min[1]	7.83	0.51	6.38	2.11	8.79**	0.94
15-min[12]	7.06	1.39	3.89	2.21	22.56***	1.72
Time-based[12]	7.33	1.09	4.35	2.02	32.30***	1.84
Event-based[1]	7.56	1.10	5.95	2.38	5.80*	0.87

[1]Significant difference between HA and CRT on post hoc
[2]Significant difference between HA and AC on post hoc
$p<0.05$*, $p<0.01$**, $p<0.001$***

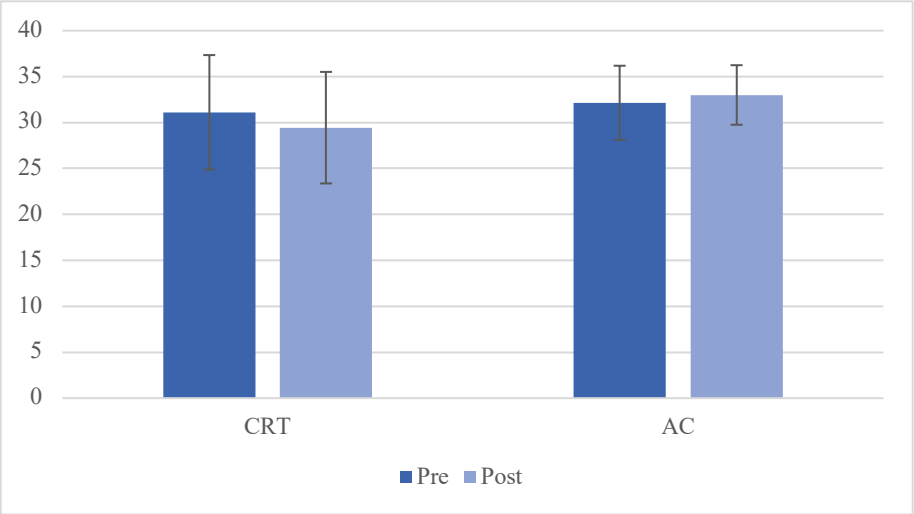

Figure 3. *Performance of the CRT and AC groups on the MIST summary score pre- and post- treatment*

Table 5. *Performance of the ABI therapy group (CRT) and active control (AC) group on the MIST pre- and post-treatment*

	CRT (n=18)						AC (n=7)					
	Pre-treatment		Post-treatment				Pre-treatment		Post-treatment			
	Mean	SD	Mean	SD	t	Cohen's d	Mean	SD	Mean	SD	t	Cohen's d
2-min	6.67	2.11	5.22	2.39	2.61	0.64	6.43	1.51	6.71	0.76	0.35	0.23
15-min	3.89	2.37	3.94	2.46	0.11	0.02	4.29	1.70	4.29	2.56	0.00	0.00
Time based	4.3	1.95	4.56	2.01	0.74	0.13	3.86	1.77	5.00	0.82	1.92	0.83
Event based	5.78	2.37	5.22	2.39	1.16	0.24	6.86	1.57	6.00	1.63	1.16	0.54

Performance of generalization measures

There were significant differences between the healthy adults and ABI individuals in both measures of generalization (WHO-QOL-Bref and CAPM) (Figure 4). ABI individuals reported significantly lower scores of the WHO-QOL- Bref (3.47 ± 0.73) indicating a self-reported lower quality of life. Fischer's LSD post hoc analysis show significant differences in the WHO-QOL-Bref, total CAPM scores, and IADL sub score between HA and CRT group; however, there was no significant differences between the HA and AC group on any generalization measures. Furthermore, there were no significant differences between either ABI group (CRT and AC) on all measures of generalization indicating that the AC group is falling between that of the HA and

CRT groups. Table 6 depicts the sub-section scores for the CAPM with significant differences present between HA and ABI groups in the IADL measure but not in the BADL measure. Overall, ABI individuals scored higher on the total, IADL, and BADL scores compared to HA indicating that they report more PM failures in their daily life.

Following treatment, the CRT group indicated a trend toward lower mean scores on all measures of generalization (Table 7), reflecting an improvement in their perception of their PM functioning and overall quality of life.

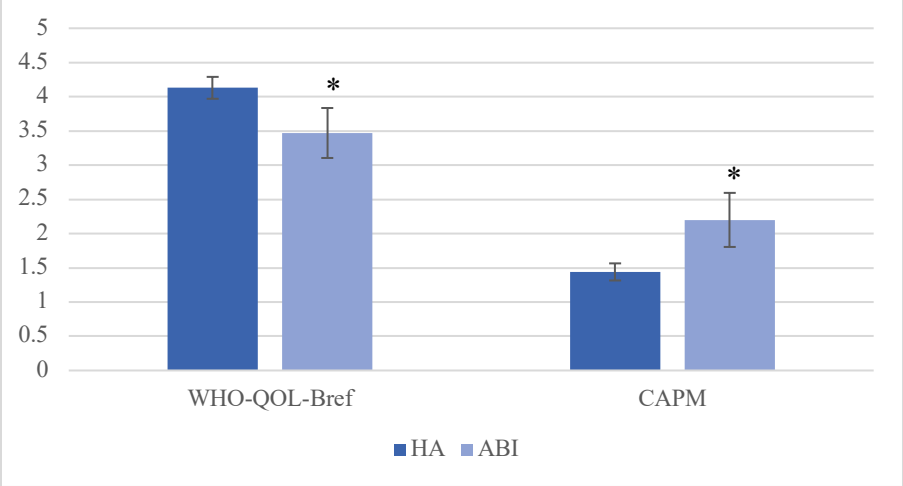

Figure 4. *HA and ABI baseline performances on WHO-QOL-Bref and CAPM generalization measures*
*Indicates significantly lower performance of ABI compared to HA

Table 6. *Generalization measures of healthy adults and ABI group prior to treatment*

	HA (n=19)		ABI (n=37)			
	Mean	**SD**	**Mean**	**SD**	**F**	**Cohen's d**
CAPM						
IADL[1]	1.57	0.30	2.21	0.90	9.16**	0.95
BADL	1.27	0.26	1.64	0.63	0.63	0.77

[1]Significant difference between HA and CRT on post hoc
$p<0.05$*, $p<0.01$**, $p<0.001$***

Table 7. *CRT and AC group performance on generalization measures pre- and post- treatment*

	CRT (n=18)						AC (n=7)					
	Pre-treatment		Post-treatment				Pre-treatment		Post-treatment			
	Mean	SD	Mean	SD	t	Cohen's d	Mean	SD	Mean	SD	t	Cohen's d
WHO-QOL-Bref	3.44	0.85	3.39	0.84	0.16	0.06	3.62	0.67	3.61	0.64	0.07	0.02
CAPM												
Total Score	2.18	0.92	2.12	0.9	0.56	0.07	1.70	0.33	1.94	0.51	2.60	0.56
IADL	2.44	1.11	2.28	1.06	1.27	0.14	1.91	0.43	2.20	0.68	1.57	0.51
BADL	1.92	0.96	1.86	0.77	0.32	0.07	1.36	0.29	1.72	0.48	1.72	0.91

Performance of neuropsychological assessment

Attention. There were significant differences between HA and ABI groups on both measures of attention, Brief Test of Attention (BTA) ($p = 0.005$) and the Digit Span ($p = 0.001$), at baseline (Figure 5). Fischer's LSD post hoc analysis revealed that ABI individuals in the CRT group performed significantly worse than healthy adults on both tests ($p < 0.05$); however, there was no significant difference between ABI individuals in the AC group and healthy adults on either test ($p > 0.05$). Additionally, there was no significant difference between the two ABI conditions on either testing measure ($p > 0.05$). Following treatment, the CRT group showed a trend towards improvement on the BTA ($p = 0.58$; Table 8). There was no significant change in either group on the Digit Span (Table 7).

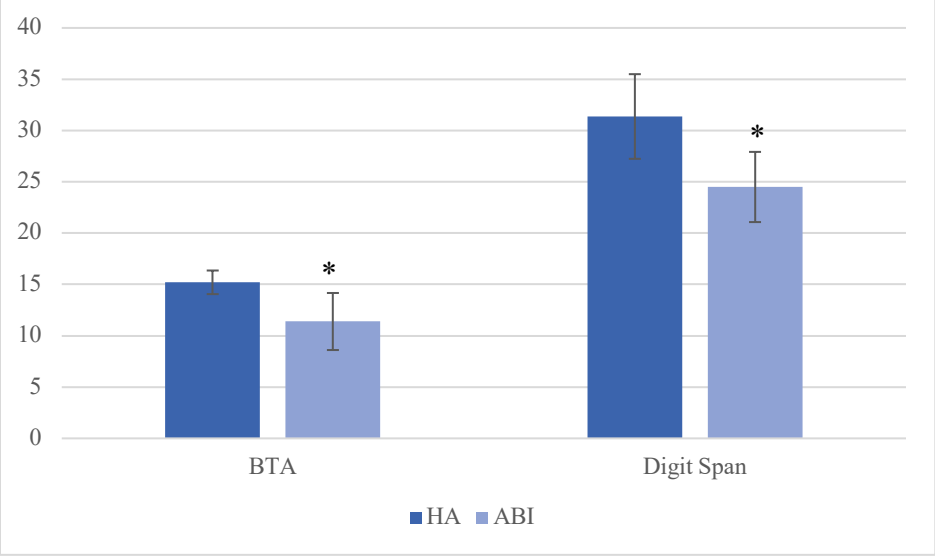

Figure 5. *HA and ABI baseline performances on the Brief Test of Attention (BTA) and Digit Span attention measures*

Table 8. *CRT and AC group performance on attention measures pre- and post- treatment*

	CRT (n=18)						AC (n=7)					
	Pre-treatment		Post-treatment				Pre-treatment		Post-treatment			
	Mean	**SD**	**Mean**	**SD**	**T**	**Cohen's d**	**Mean**	**SD**	**Mean**	**SD**	**T**	**Cohen's d**
BTA	11.39	5.56	13.06	4.22	2.031	0.338	12.71	4.46	11.14	3.53	1.220	0.390
Digit Span	24.50	6.84	24.78	7.12	0.246	0.040	25.43	3.21	25.57	4.24	0.106	0.037

Retrospective Memory. There were significant differences between HA and ABI groups on total scores for both measures of retrospective memory, HVLT-R ($p = 0.001$) and the BVMT-R ($p = 0.000$), at baseline (Figure 6). There were significant differences between HA and ABI groups on all sub-sections of both HVLT-R and BVMT-R, except for the BVMT-R Learning measure in which no significant differences were found (Table 9). Fischer's LSD post hoc analysis revealed that ABI individuals in both the CRT and AC group performed significantly worse than healthy adults on all measures of both tests (excluding BVMT-R Learning measure) ($p<0.05$); however, there was no significant difference between ABI individuals in the AC group and healthy adults on the percent retained measure of the BVMT-R ($p>0.05$). This indicates ABI individuals in the AC group received scores that fall between that of HA and ABI individuals in the CRT group on the retention measure of the BVMT-R. After treatment, ABI individuals in the CRT group had significantly higher total recall scores on the BVMT-R (Table 10).

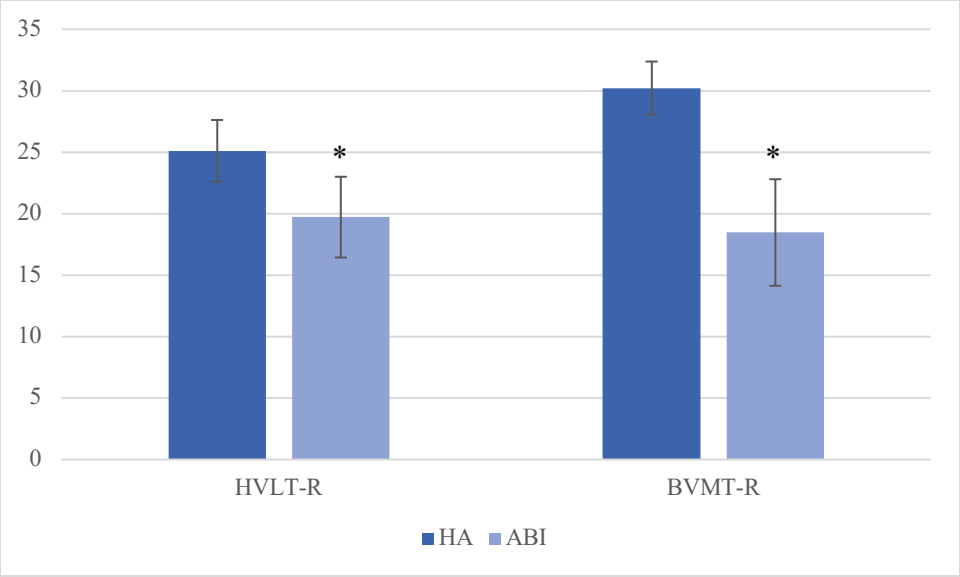

Figure 6. *HA and ABI baseline performances on the HVLT-R and BVMT-R retrospective memory measures*

Table 9. *HA and ABI baseline performances on sub scores of the HVLT-R and BVMT-R*

	HA (n=19)		ABI (n=25)			
	Mean	**SD**	**Mean**	**SD**	**F**	**Cohen's d**
HVLT-R						
Delayed Recall[12]	9.00	2.05	5.67	4.03	17.65***	1.04
Retention[12]	88.12	13.82	64.39	36.66	13.35**	0.86
Recognition Discrimination[12]	11.47	1.12	9.35	3.00	8.75**	0.94
BVMT-R						
Trial 1[12]	7.94	2.60	4.35	2.34	24.02***	1.45
Learning	3.61	2.45	3.65	2.06	0.07	0.02
Percent Retained[1]	99.54	3.54	74.10	33.20	8.63**	1.08

[1]Significant difference between HA and CRT on post hoc
[2]Significant difference between HA and AC on post hoc
$p<0.05$*, $p<0.01$**, $p<0.001$***

Table 10. *CRT and AC group performance on retrospective memory measures pre- and post- treatment*

	CRT (n=18)						AC (n=7)					
	Pre-treatment		Post-treatment				Pre-treatment		Post-treatment			
	Mean	**SD**	**Mean**	**SD**	**t**	**Cohen's d**	**Mean**	**SD**	**Mean**	**SD**	**t**	**Cohen's d**
HVLT-R												
Total Recall	19.72	6.57	20.61	6.06	0.65	0.14	19.00	5.47	20.14	5.46	0.85	0.21
Delayed Recall	5.67	4.03	6.11	3.44	0.58	0.12	4.29	3.77	3.71	4.11	0.35	0.15
Retention	64.39	36.66	72.72	32.32	0.99	0.24	47.86	34.87	39.27	35.87	0.59	0.24
Recognition discrimination	9.35	3.00	8.13	3.24	1.66	0.39	8.43	3.21	8.57	3.87	0.28	0.04
BVMT-R												
Trial 1	4.35	2.34	5.24	2.31	1.82	0.38	4.00	3.21	5.14	3.24	1.80	0.35
Total Recall	18.47	8.67	22.35	7.18	5.27*	0.49	16.57	9.47	19.43	10.66	1.24	0.28
Learning	3.65	2.06	4.06	1.92	0.69	0.21	3.14	1.95	2.86	1.95	0.60	0.14
Percent Retained	74.10	33.20	80.2	32.06	0.26	0.19	93.39	19.54	89.48	16.87	0.49	0.21

*Indicates significant increase post-therapy ($p<0.05$)

Executive Function. There were significant differences between HA and ABI groups on total scores for all measures of executive function, Animal Naming ($p =0.000$), COWAT ($p=0.039$), and the Stroop ($p=0.001$), at baseline (Figure 7; Table 11). There were significant differences between HA and ABI individuals on each sub-section scores of the Stroop; however, there was not a significant difference between HA and the AC group on the color-word score (Table 11). Fischer's LSD post hoc analysis revealed that ABI individuals performed significantly worse than healthy adults on all measures of the Stroop ($p<0.05$); however, there was no significant difference between ABI individuals in the AC group and healthy adults on color-word score sub-section (Table 11). There were no significant changes on any of the tests for executive function in either group following treatment (Table 12).

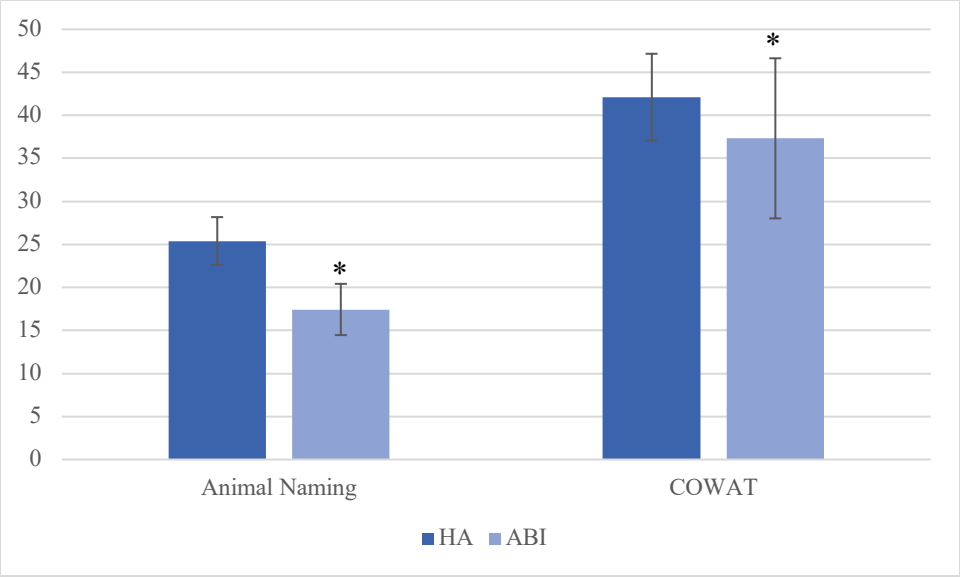

Figure 7. *HA and ABI baseline performances on the Animal Naming and COWAT executive function measures*

Table 11. *HA and ABI baseline performances on the Stroop*

	HA (n=19)		ABI (n=25)			
	Mean	**SD**	**Mean**	**SD**	**F**	**Cohen's d**
Stroop						
Word score[12]	47.10	9.71	65.27	16.25	13.80***	1.36
Color Score[12]	63.06	9.15	92.69	26.84	11.92***	1.48
Color-word score[1]	98.39	21.57	158.46	66.30	13.71***	1.22

[1]Significant difference between HA and CRT on post hoc
[2]Significant difference between HA and AC on post hoc
p<0.05*, p<0.01**, p<0.001***

Table 12. *CRT and AC group performance on executive function measures pre- and post- treatment*

	CRT (n=18)						AC (n=7)					
	Pre-treatment		Post-treatment				Pre-treatment		Post-treatment			
	Mean	**SD**	**Mean**	**SD**	**t**	**Cohen's d**	**Mean**	**SD**	**Mean**	**SD**	**t**	**Cohen's d**
Animal Naming	17.44	5.96	19.33	12.06	0.74	0.20	18.00	6.68	17.86	5.81	0.08	0.02
COWAT	37.33	18.61	36.67	16.56	0.18	0.04	32.71	12.91	32.71	11.87	0.00	0.00
Stroop												
Word score	65.27	16.25	71.76	20.38	1.39	0.35	64.43	12.64	76.63	42.29	1.04	0.39
Color Score	92.69	26.84	101.65	27.96	1.51	0.33	117.00	93.57	104.44	77.71	1.52	0.15
Color-word score	158.46	66.30	158.86	64.46	0.03	0.01	132.97	62.56	145.51	64.02	1.01	0.20

Mood. There were significant differences between HA and ABI groups both mood assessments, the Beck Anxiety Inventory (BAI) (p =0.005) and the Beck Depression Inventory (BDI) (p=0.000), at baseline (Figure 8). Both the AC and CRT groups had higher scores on each assessment indicating a higher level of anxiety and depression. There were no significant changes in either group following treatment (Table 13).

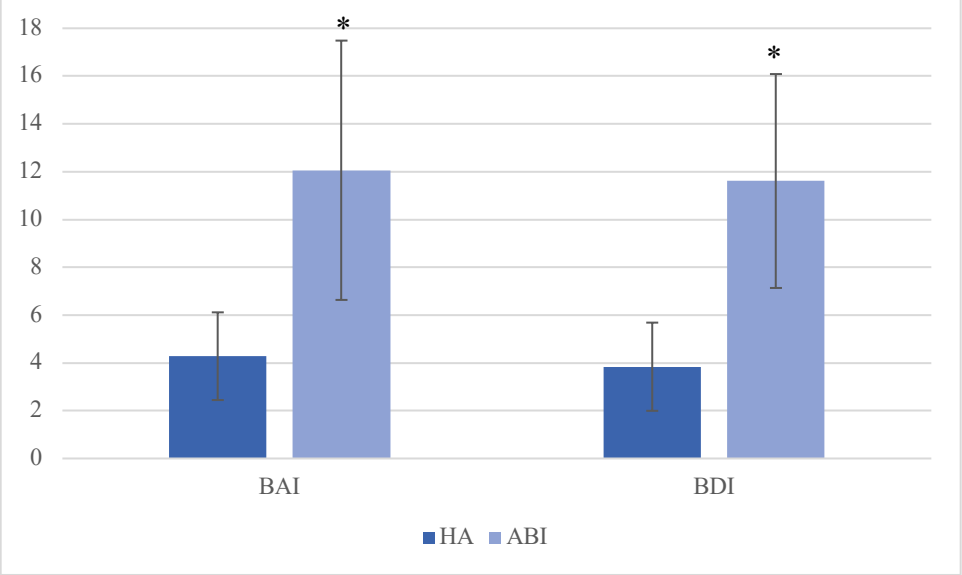

Figure 8. *HA and ABI baseline performances on the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) mood measures*

Table 13. *CRT and AC group performance on mood measures pre- and post- treatment*

	CRT (n=18)						AC (n=7)					
	Pre-treatment		Post-treatment				Pre-treatment		Post-treatment			
	Mean	SD	Mean	SD	t	Cohen's d	Mean	SD	Mean	SD	t	Cohen's d
BAI	12.06	10.85	13.17	13.48	0.78	0.09	7.71	4.96	8.14	5.81	0.22	0.08
BDI	11.61	8.95	12.06	10.85	0.62	0.05	11.86	7.24	13.29	8.97	1.18	0.18

Performance. There was a trend towards score improvement on the CAPM generalization measure, BTA attention measure, the HVLT-R retrospective memory measures, and all three measures of executive function (Table 14). There was a significant difference in the improvement of CRT group's retrospective memory score on the BVMT-R compared to pre-

therapy (Table 14). In the AC condition there is an observed improvement of individuals on the HVLT-R retrospective memory measure as well as the BAI mood measure; however, neither are statistically significant changes.

Table 14. *Percent breakdown of CRT and AC group performance on all measures*

		CRT (n=18)			AC (n=7)		
		Improved (%)	**Declined (%)**	**Same (%)**	**Improved (%)**	**Declined (%)**	**Same (%)**
Prospective Memory	**MIST**	44.5	44.5	11	43	14	43
Generalization	**WHO-QOL-Bref**	39	56	6	29	57	14
	CAPM	56	44	0	29	71	0
Attention	**BTA**	56	28	17	14	43	43
	Digit Span	28	44	28	43	57	0
Retrospective Memory	**HVLT-R**	67	28	6	71	29	0
	BVMT-R	88*	12	0	24	12	14
Executive Function	**Animal Naming**	50	44	6	43	57	0
	COWAT	56	33	11	43	43	14
	Stroop	59	41	0	43	57	0
Mood	**BAI**	33	56	11	71	29	0
	BDI	44	50	6	33	50	17

*****Statistically significant improvement ($p<0.05$)

Functional MRI Measures

The brain regions that exhibited strong statistical evidence for activation ($p<0.05$) during PM trials compared to the ongoing task (combined straight and curvy control trials), for healthy adults (HA) and ABI individuals are represented in Tables 15-19. There was no evidence for Time 1 vs. Time 2 change; therefore, no indication that brain activation changes post treatment. Figure 8 represents the extent to which groups significantly differ in the amount to which their

BOLD activity is different on PM trials compared with straight and curvy control condition trials.

Table 15. *Parcels in which HA activation is higher than ABI participant activation in the Visual Regions*

Parcel Name		Hemisphere	Region	*t*	*p*
Area V3A	V3A	Right	Dorsal Stream Visual Cortex	2.12	0.023
Area V3B	V3B	Right	Dorsal Stream Visual Cortex	1.78	0.042
Eighth Visual Area	V8	Right	Ventral Stream Visual Cortex	1.77	0.044
Fusiform Face Complex	FFC	Right	Ventral Stream Visual Cortex	2.21	0.018
VentroMedial Visual Area 3	VMV3	Right	Ventral Stream Visual Cortex	2.84	0.005
VentroMedial Visual Area 3	VMV3	Left	Ventral Stream Visual Cortex	2.17	0.015
Area PH	PH	Right	MT+ Complex and Neighboring Visual Areas	2.49	0.008
Area V4t	V4t	Left	MT+ Complex and Neighboring Visual Areas	2.82	0.004

Table 16. *Parcels in which HA activation is higher than ABI participant activation in the Temporal and Parietal Region*

Parcel Name		Hemisphere	Region	*t*	*p*
Area TE1 posterior	TE1p	Right	Lateral Temporal Cortex	1.92	0.034
Lateral Area 7P	7Pl	Right	Superior Parietal Cortex	1.79	0.043
Area Lateral IntraParietal ventral	LIPv	Right	Superior Parietal Cortex	1.69	0.049
Medial IntraParietal Area	MIP	Right	Superior Parietal Cortex	1.81	0.040
Lateral Area 7P	7Pl	Left	Superior Parietal Cortex	1.84	0.035
Area IntraParietal 1	IP1	Left	Inferior Parietal Cortex	2.17	0.019
Area IntraParietal 0	IP0	Left	Inferior Parietal Cortex	1.91	0.031

Table 17. *Parcels in which ABI participant activation is higher than HA activation in the Cingulate Region*

Parcel Name		Hemisphere	Region	*t*	*p*
Parieto-Occipital Sulcus Area 1	POS1	Left	Posterior Cingulate Cortex	1.82	0.044
Area ventral 23 a+b	v23ab	Left	Posterior Cingulate Cortex	1.71	0.046
Area p32 prime	p32pr	Right	Anterior Cingulate and Medial Prefrontal Cortex	2.29	0.014
Area Posterior 24 prime	p24pr	Left	Anterior Cingulate and Medial Prefrontal Cortex	2.26	0.016
Anterior 24 prime	a24pr	Left	Anterior Cingulate and Medial Prefrontal Cortex	1.90	0.030
Area p32 prime	p32pr	Left	Anterior Cingulate and Medial Prefrontal Cortex	2.68	0.005
Area a24	a24	Left	Anterior Cingulate and Medial Prefrontal Cortex	2.21	0.018
Area dorsal 32	d32	Left	Anterior Cingulate and Medial Prefrontal Cortex	2.09	0.023
Area p32	p32	Left	Anterior Cingulate and Medial Prefrontal Cortex	2.09	0.025
Area anterior 32 prime	a32pr	Left	Anterior Cingulate and Medial Prefrontal Cortex	2.06	0.024

Table 18. *Parcels in which ABI participant activation is higher than HA activation in the Frontal and Insula/Frontal Operculum Regions*

Parcel Name		Hemisphere	Region	*t*	*p*
Area 47s	47s	Right	Orbital and Polar Frontal Cortex	2.59	0.005
Area 10d	10d	Left	Orbital and Polar Frontal Cortex	1.90	0.036
Polar 10p	10pp	Left	Orbital and Polar Frontal Cortex	2.06	0.026
Area 47s	47s	Left	Orbital and Polar Frontal Cortex	2.75	0.004
Area 9 anterior	9a	Right	DorsoLateral Prefrontal Cortex	2.18	0.021
Area 9 anterior	9a	Left	DorsoLateral Prefrontal Cortex	2.11	0.023
Posterior Insular Area 2	PoI2	Right	Insular and Frontal Opercular Cortex	1.97	0.031
Pirform Cortex	Pir	Right	Insular and Frontal Opercular Cortex	1.96	0.029
Anterior Agranular Insula Complex	AAIC	Right	Insular and Frontal Opercular Cortex	2.10	0.023
Frontal OPercular Area 3	FOP3	Right	Insular and Frontal Opercular Cortex	2.50	0.009
Area Posterior Insular 1	PoI1	Right	Insular and Frontal Opercular Cortex	1.85	0.038
Insular Granular Complex	Ig	Right	Insular and Frontal Opercular Cortex	2.26	0.014
Frontal OPercular Area 4	FOP4	Left	Insular and Frontal Opercular Cortex	2.30	0.015
Area Frontal Opercular 5	FOP5	Left	Insular and Frontal Opercular Cortex	1.79	0.041

Table 19. *Parcels in which ABI participant activation is higher than HA activation in the Sensory/Motor, Auditory, Temporal, and TPO Junction Regions*

Parcel Name		Hemisphere	Region	*t*	*p*
Ventral Area 24d	24dv	Right	Paracentral Lobular and Mid Cingulate Cortex	1.85	0.036
Supplementary and Cingulate Eye Field	SCEF	Right	Paracentral Lobular and Mid Cingulate Cortex	2.03	0.025
Area 6mp	6mp	Left	Paracentral Lobular and Mid Cingulate Cortex	2.15	0.021
Ventral Area 6	6v	Right	Premotor Cortex	2.10	0.026
Rostral Area 6	6r	Right	Premotor Cortex	2.95	0.003
Area OP4/PV	OP4	Right	Posterior Opercular Cortex	2.03	0.027
Area PFcm	PFcm	Right	Posterior Opercular Cortex	2.13	0.022
Frontal Opercular Area 1	FOP1	Right	Posterior Opercular Cortex	2.35	0.013
Area OP4/PV	OP4	Left	Posterior Opercular Cortex	1.74	0.047
Area PFcm	PFcm	Left	Posterior Opercular Cortex	1.99	0.030
Medial Belt Complex	MBelt	Right	Early Auditory Cortex	2.28	0.013
Lateral Belt Complex	LBelt	Right	Early Auditory Cortex	1.71	0.045
RetroInsular Cortex	RI	Left	Early Auditory Cortex	2.00	0.025
Auditory 4 Complex	A4	Right	Auditory Association Cortex	1.87	0.034
Hippocampus	H	Left	Medial Temporal Cortex	1.76	0.049
ParaHippocampal Area 2	PHA2	Left	Medial Temporal Cortex	2.04	0.030
Area TG Ventral	TGv	Left	Lateral Temporal Cortex	2.22	0.017
PeriSylvian Language Area	PSL	Left	Temporo-Parieto-Occipital Junction	2.12	0.021
Area TemporoParietoOccipital Junction 1	TPOJ1	Left	Temporo-Parieto-Occipital Junction	2.38	0.012
Area PF Complex	PF	Right	Inferior Parietal Cortex	2.11	0.023

Figure 9 depicts the differences in brain activation between healthy adults and individuals with ABI during the memory trials (PM) compared to the control trials (straight and curvy). Therefore, the maps in the image represent the extent to which groups significantly differ in the amount to which their BOLD activity is different on PM trials compared with ongoing trials. This comparison pinpoints regions-of-interest through parcels in which HA activation is higher than ABI participants' activation (ABI<HA). These are in the visual region (dorsal stream visual cortex, ventral stream visual cortex, MT+ complex and neighboring visual areas), parietal region

(superior and inferior parietal cortex), and temporal regions (lateral temporal cortex). Figure 9 also indicated the parcels in which ABI activation is higher than HA participants' activation (ABI>HA). These are in the cingulate region (posterior cingulate cortex and anterior cingulate and medial prefrontal cortex), frontal and insula/frontal operculum regions (orbital and polar frontal cortex, dorsolateral prefrontal cortex, insular and frontal opercular cortex), sensory-motor region (paracentral lobular and mid cingulate cortex, posterior opercular cortex, premotor cortex), auditory (early auditory cortex, auditory association cortex), temporal region (medial and lateral Temporal Cortex), parietal cortex (inferior parietal cortex), and TPO junction region (Temporo-Parieto-Occipital Junction).

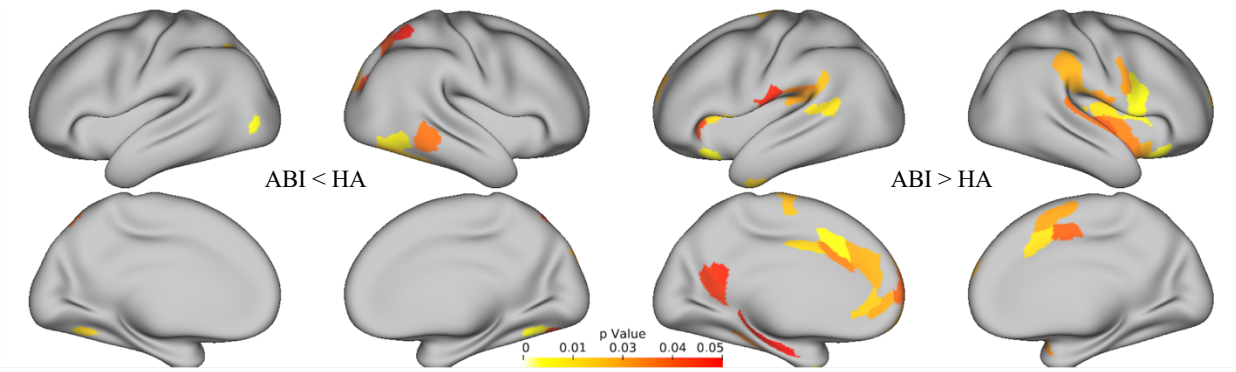

Figure 9. *Difference in BOLD Activity of PM trials compared to Control Condition*
*yellow indicates strong statistical evidence for activation; red indicates weak statistical evidence for activation

DISCUSSION

The aim of this study was to evaluate what brain areas were activated during PM task stimuli in adults with ABI compared to healthy adults and measure the efficacy of cognitive rehabilitation in improving PM function. Additionally, the fMRI post-scan was used to determine if there were changes in brain activation during the PM task following CRT compared to pre-therapy. While the results of this study support the hypothesis that at baseline individuals with ABI score significantly lower than HA individuals on standardized measures of PM, cognitive

rehabilitation did not appear to improve PM function as anticipated. Following rehabilitation therapy, neither the CRT group or AC group showed improvement of the MIST, and the only significant improvement observed in memory assessment was the total score on the BVMT-R, indicating modest improvement in visuospatial retrospective memory. This study was predominantly limited by the small sample size which resulted from recruitment and retention difficulties in the participant population.

Neuropsychological Assessments

Pre-testing assessments indicate that ABI individuals in the CRT group show significantly lower mean scores ($p<0.05$) compared to HA results on all measures of memory, including MIST, HVLT-R, and BVMT-R. However, pre-testing assessment only indicated a significant difference between the ABI individuals in the AC group and HA in particular sub-scores including MIST summary, time-based and 15-minute delay scores, all sub-scores of the HVLT-R, and BVMT-R trial 1 and total recall. Overall, this indicates a lesser memory impairment in the AC group than the CRT group. This could create a skew in the data analysis as the AC group demonstrates a higher functioning than the CRT group.

ABI individuals in the CRT group reported a significant difference when compared to HA in all standardized assessments except the measure of executive function, Controlled Oral Word Association Test (COWAT). Furthermore, there was a significant difference in both ABI groups (CRT and AC) compared to HA in the Stroop, BDI, and Animal Naming assessments. This difference indicates an impairment in these functions for individuals in the CRT group; however, there was more variability in AC and HA comparison which may result in a bias. These results indicate a significant cognitive impairment in individuals with ABI; however, the AC group results indicate higher functioning in that group compared to the CRT group. With highest

self- reports being that of memory impairment, cognitive processes such as attention and executive function are key components in the memory processing network of the brain.

This preliminary data stresses the need for cognitive rehabilitation strategies to help improve areas of cognitive impairment and overall quality of life. These results support the hypothesis that at baseline individuals with ABI will score significantly lower than HA individuals on standardized measures of prospective memory as well as on the assessments of memory, attention, and executive functions and on measures of generalization and quality of life.

Cognitive Rehabilitation Assessment

Following cognitive rehabilitation, there was only a significant increase in performance on the retrospective memory assessment ($p=0.000$), the Brief Visuospatial Memory Test (BVMT-R). There was no significant change in either ABI groups on other cognitive assessments, failing to support our hypothesis that the CRT group would perform better on the neuropsychogical battery post-therapy in comparison to the AC group. However, over fifty percent of the participants in the CRT group improved on seven of the twelve neuropsychological measures (Table 14); while improvement over the fifty percent mark in the AC group was only seen on two of the twelve measures. This data suggests a trend towards improved functioning in the CRT group however not enough to provide significant differences.

The sample size and heterogeneity of the participant population most likely contributed to the failure to show significant improvement post-therapy. Furthermore, it is likely that the once a week for six-week cognitive rehabilitation design demonstrates improvement in compensatory approaches for enhancement of PM functioning; however, a restorative approach may need a more rigorous design, requiring individuals to undergo rehabilitation for consecutive days for a

longer period of time with each visit. Further research will be required to determine a more effective approach to restorative rehabilitation and potential cortical reorganization.

Physiological Assessment

There was strong statistical evidence in Figure 9 demonstrating the comparison which pinpoints regions-of-interest through parcels in which HA activation is higher than ABI participants' activation (HA>ABI). Specifically, these regions include sub-regions of the visual cortex, parietal, sensory-motor and temporal regions. This decreased activation in ABI individuals support our hypothesis indicating an impairment in PM function in individuals with ABI. Conversely, there was strong statistical evidence indicated in which the parcels of ABI activation was higher than HA participants activation (ABI>HA). Specifically, these regions-of-interest included sub-regions of the cingulate region, frontal and insula/frontal operculum regions, sensory-motor region, auditory region, temporal region, and TPO junction region. This indicated that individuals with ABI are working harder that HA to process the intended action.

The strong statistical evidence of activation mediated by prospective memory performance in the dorsolateral prefrontal, inferior parietal, and posterior cingulate agrees with findings from Burgess et al. (2001). The most prominent findings of PM paradigms are associated with activation in the prefrontal cortex. Particularly, performance of PM tasks relative to an ongoing task is associated with the activation of lateral aspects of the rostral prefrontal cortex (BA10). Burgess et al. (2001) also found that during event-based prospective memory tasks there tends to be an increased activation of the lateral aspects of the rostral prefrontal cortex during periods where participants are maintaining an intention, whether a prospective memory cue is encountered, or the intended action is enacted. Our data clearly shows a higher activation

in the prefrontal regions of the ABI individuals indicating that there is more brain activity for the PM task in this group (i.e. they are working harder to perform the same task as the HA).

There were no differences in BOLD activation from baseline scans to post-therapy scans, failing to support the hypothesis that that brain activation in the dorsomedial frontal gyrus, anterior cingulate, and bilateral putamen regions-of-interest will increase relative to pre-therapy baseline levels for ABI participants in CRT and brain activation in ventromedial frontal gyrus will decrease compared to the AC. This is consistent with cognitive and behavioral measures as PM performance change was not found in the neuropsychological assessments post-therapy.

Limitations

The sample size was a large limitation on for this study. Despite recruiting emails sent regularly to healthcare providers, leaders of support groups, social workers, and nonprofit organizations associated with the ABI population in the area, it was difficult to find participants for the study. Due to the exclusion criteria and length of the study, many individuals recruited were unable to participate or dropped out at some point during the six weeks of therapy. Additionally, uniform testing periods were not kept for all participants. Due to holidays, dependency on others for transportation, and overall fatigue and mental health, appointments were periodically rescheduled or postponed resulting in a variation of time in between each session.

Heterogeneity in the participant population also posed a limitation in the study. In the ABI group there was variability in the etiology and time since injury, as well as type and degree of impairments. Variability in ages between the ABI group and HA group may have contributed to the differences seen in the baseline data (CRT: 45.7±11.5; AC: 46.6±11.1; HA: 29.2±7.4). The CRT and AC groups of ABI individuals were not significantly different but they both were

significantly different than the HA age group. HA being significantly younger than the CRT could result in confounding variability and further research will need to be collected to assess an equal age distribution. Lastly, post hoc multiple comparison analysis revealed that the ABI individuals in the AC group did not differ significantly from neither the CRT group or the HA group, indicating that the AC group was composed of individuals lying somewhere between the two condition with regards to their performance and demonstrated deficits. It is important that the AC group did not differ from the CRT group; however, the fact that they did not differ from the HA group on multiple measures indicate that their impairment is less severe than that of the individuals randomly assigned to the CRT group.

Finally, there was a problem with a denoising step in the fMRI scans during the preliminary period of the study. Upon fMRI data analysis, a glitch was discovered in the Institute of Living linux fMRI data processing system. It looked like data was being processed, when in fact it got about 3/4 of the way through and stopped on a complex de-noising step. Due to an e-prime + scanner glitch, behavioral responses were not recorded. This unfortunately means that we were unable to look at correct versus incorrect responses. Therefore, the comparison analyzed the activation during the trial meaning that brain activity was being recorded and compared between the control and PM trials, but the accuracy of the test was not recorded for over half of the participants that underwent an fMRI. Furthermore, limited significance in brain activation seem to be a result of an over aggressive data cleaning algorithm applied to the most recent analysis.

Future Direction

An altered intervention design may be more desirable for a comprehensive cognitive rehabilitation plan centered on a restorative approach to PM function. Providing a more intensive

therapy commitment over the span of a few days my provide different results than a less concentrated approach over the span of weeks. It is possible that six hours of therapy regimented over a breath of time is not sufficient to induce noticeable changes. It would also be useful to add a longitudinal component and assess individuals six months or one year following completion of therapy to measure long-term efficacy of the cognitive rehabilitation.

CONCLUSION

The behavioral results of this study provide significant evidence of impairment in particular cognitive areas such as prospective memory, executive function, and attention for individuals with acquired brain injury and display a baseline difference between healthy adults and ABI individuals. Results indicate that cognitive rehabilitation may lead to improvements in memory function in ABI individuals. Although cognitive rehabilitation did not lead to significant improvements on the MIST, a clinical measure of PM, individuals reported improvements in PM in daily life and retrospective memory measures showed significant improvement post-therapy. The neuroimaging results support the hypothesis that regions of interest are activated during a PM task and vary in brain activation between healthy adults and individuals with ABI. Results gave no suggestion to cortical changes post-therapy which are consistent with behavioral findings. Increasing the sample size and altering the duration of the cognitive rehabilitation would likely lead to a more conclusive and potentially more effective rehabilitation plan. Due to the importance of PM functioning in daily life, further research into the improvement in PM function in ABI individuals in imperative for the independence and quality of life in this population.

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