Cover Sheet

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Protocol

1. Project Title:

Combining attention and metacognitive training to improve goal directed behavior in Veterans with TBI

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3. Abstract:

Background: Traumatic Brain Injury (TBI) can be the beginning of a disease process that produces change that continue years after injury resulting in debilitating chronic TBI symptomatology. Some studies find that up to 30% of people that have sustained mild traumatic brain injury (mTBI) have persistent symptoms. Enduring cognitive deficits after mTBI present barriers to full functional recovery and re-entry into societal roles. Executive dysfunction, poor attention-concentration, and memory difficulties are the most persistent disabilities faced by mTBI survivors. An estimate 44% of Veterans with mTBI also have post-traumatic stress disorder (PTSD) with overlapping symptoms. Attention problems are reported by 50% of combat Veterans which are requisite for other cognitive processes that are vital to everyday functioning such as memory, problem solving, language skills, and the cognitive control of behavior. Effective interventions are needed to address the cognitive deficits resulting from chronic mTBI. Of the attention and executive function treatments currently used in clinical practice, there is a dearth of those with substantial evidence to support effectiveness. Current cognitive interventions for Veterans with mTBI did not include specific attention training, lacked rigorous training or found improvement only on self-reported symptoms. In order to improve translation, strategy training has been recommended to accompany attention training. Goal Management Training (GMT) is such a strategy training and has been found to be improve executive function skills in Veterans with mTBI. However, GMT lacks specific attention training, which is a limitation in that attention is a component of the normal executive function used in goal management. Given the need in mTBI lack of rigor in attention training, the relationship of attention to goal management, and the promise of combined attention training and goal

management training, we will innovatively combine the metacognitive intervention, GMT, with a drill method of attention training that also includes individual functional goals for attention recovery.

Method: This is a randomized control pilot study to determine effectiveness of GMT plus Attention Training in 50 Veterans with mTBI. The research design is a parallel study with randomization to treatment or control with test administration at pre/post and six months following treatment. A multiple linear regression model will be used to determine if there is a significant association between treatment effect and comorbidities such as PTSD, depression, anxiety, pain, sleep, substance abuse, etc.

4. Background:

Problem. TBI can be the beginning of a disease process that produces change that continue years after injury resulting in debilitating chronic TBI symptomatology[1, 2]. Some studies find that up to 30% of people that have sustained mTBI have persistent symptoms[3]. Persistent symptoms following mTBI have been related to diffuse axonal injury[4] or neuroinflammatory reactions[5]. Enduring cognitive deficits after mTBI present barriers to full functional recovery and re-entry into societal roles. Executive dysfunction, poor attention-concentration, and memory difficulties are the most persistent disabilities faced by mTBI survivors[6, 7]. An estimate 44% of Veterans with mTBI also have PTSD[8] with overlapping symptoms. Attention problems are reported by 50% of combat Veterans[9] which are requisite for other cognitive processes that are vital to everyday functioning such as memory, problem solving, language skills, and the cognitive control of behavior. Associated comorbidities also impair cognition making it difficult to diagnose and treat Veterans with mTBI. These comorbidities include pain[10], substance abuse[11], anxiety[12], depression[13], fatigue[14] and sleep disturbances[15] that also specifically impact attention. Cognitive deficits are the most debilitating following mild to severe TBI and can lead to long-term disability and immense economic burden[16].

Gaps in Knowledge.

Studies of training and response to treatment. Effective interventions are needed to address the cognitive deficits resulting from chronic mTBI. Of the attention and executive function treatments currently used in clinical practice, there is a dearth of those with substantial evidence to support effectiveness[17]. Most studies were conducted for moderate to severe TBI. Recent studies in Military and Veterans with mTBI reported improvement following cognitive rehabilitation[18-23]; but there were study limitations with remaining serious gaps in knowledge. For example, there was absence of rigor in attention training. Cognitive interventions did not include specific attention training[23] or the attention training consisted of simply “paying attention during conversations”[19, 22]. The time spent engaged in attention training was frequently not reported[19, 21, 22]. Some studies found improvement only in subjective self-report of symptoms or lacked improvement in objective cognitive tests[18-21]. Finally, training methods have not specifically targeted the orienting component of attention that is problematic for Veterans with mTBI[24-26]. Some studies of attention training have shown some improved attention on laboratory measures, but, unfortunately, limited translation to improvement of real-world task performance[27].

In order to improve translation, strategy training has been recommended to accompany attention training[28]. Goal Management Training (GMT) is such a strategy training designed to improve cognition regardless of etiology. GMT is a manualized, interactive, psychoeducational meta-strategy intervention designed to promote a mindful approach to complex real-life tasks and reduce lapses of attention in brain-injury survivors[29-31]. Additionally, GMT employs some compensatory strategies for achieving goals, which is recommended as an effective cognitive treatment by an international panel of experts in cognitive therapy (INCOG)[32]. A recent study showed benefits of combining attention and compensatory training in pediatrics[33]. GMT is a promising intervention, and effect size improved when combined with personal goal setting or problem solving[34]. We recently demonstrated executive function improvement in Veterans with chronic blast-related mild TBI in response to GMT, finding significant improvement in executive function, according to the Computerized Tower of London (cTOL)[35, 36]. However, GMT lacks rigorous attention training, which is a limitation in that attention is a necessary component of the normal executive function needed for goal management.

Given the need in mTBI, lack of rigor in attention training, the relationship of attention to goal management, and the promise of combined attention training and goal management training; we will combine the metacognitive intervention, GMT, with a drill method of attention training that also includes individual functional goals for attention recovery.

5. Specific Aims:

<u>Effective interventions for attention and executive function for Veterans dealing with pervasive symptoms following mild traumatic brain injury (mTBI) are desperately needed.</u> Veterans with mTBI and Posttraumatic Stress Disorder (PTSD) experience cognitive and emotional barriers that interfere with the ability to fully participate in societal roles. Specifically, both mTBI and PTSD are associated with altered attention[25, 37] which is the gateway to executive function and other cognitive processes. Of the few available cognitive training studies for Veterans with mTBI and PTSD there are several shortcomings. First, cognitive interventions have failed to rigorously train attention and have not specifically targeted the orienting component of attention that is problematic for Veterans with mTBI and PTSD[25, 26]. Second, neuropsychological test findings have been mixed and do not consistently demonstrate improvement. Third, in many studies, there is reliance on self-report measures to attempt to demonstrate effectiveness. Nevertheless, studies of attention training have shown some improved attention on laboratory measures but unfortunately have limited translation to improvement of real-world tasks[27]. To improve translation, strategy training has been recommended to accompany attention training[28]. In our preliminary work we tested feasibility and potential for a strategy intervention entitled Goal Management Training (GMT) finding significant improvements in executive function, according to the Computerized Tower of London (cTOL).

Given the in-laboratory success of attention training, the prior failure of attention training to translate to real-world tasks, and the feasibility and promise of Goal Management Training, we will innovatively combine attention and Goal Management Training. This

combination has the potential to not only improve the gateway to executive function but facilitate implementation of attention strategies into functional behavior. Outcomes of Veterans with mTBI (25 treatment/25 control) will be measured with objective neuropsychological tests of attention and executive function, as well as real-world task performance.

Aim 1: Determine the treatment effect of attention training combined with GMT in Veterans with mTBI.

Hypothesis 1: GMT plus attention training will significantly improve performance on tests of cognition compared to the control group.

Primary measure: Computerized Tower of London (cTOL) total time, time to first move and optimal moves). We have found significant improvement in cTOL following GMT in previous cohorts of Veterans with blast-related mTBI and anticipate improvement following a combined intervention.

Secondary measure: Attention Network Task (ANT) reaction time and errors for one or all dissociable components of three attentional systems (orienting, alerting, executive control) following intervention. There is little understanding of components of impaired attention and how it impacts executive function; therefore, there is limited guidance in shaping cognitive training. We will conduct an experimental task (attention network task) that disassociates three attentional components (alerting, orienting, and executive control). We will specifically target the orienting component of attention that is problematic for Veterans with mTBI and PTSD[24, 26]. Attentional processes are vital to goal-directed behavior. There is great potential in the use of these measures to identify individual differences (type of attention deficit) that could moderate treatment-related improvement and inform targeted interventions.

Hypothesis 2: Treatment gains will translate to functional activities compared to controls.

Primary measure of functional performance: test of grocery shopping skills (TOGSS) total time and optimal strategy use. The TOGSS captures efficiency in completing a real-world task and aligns with the strategy skills learned in GMT.

Secondary measure of community participation, the *Community Reintegration of Servicemembers* (CRIS) extent of participation. The CRIS demonstrated significant GMT treatment effect compared to controls in Veterans with mTBI. The combined treatment of attention training using drill training and implementing strategies to improve attention in a functional setting through GMT will potentiate treatment effect to functional activities. Measuring functional improvement through performance-based measures and self-report of engagement in activities will demonstrate treatment translation.

Tertiary analysis will be conducted on moderator variables: *PTSD symptoms, Pain, History of Substance Abuse, Depression, number of concussions and combat exposure.*

Successful completion of the proposed study will provide insight into the effectiveness of the innovative combined treatment of attention and executive function in Veterans with mTBI and PTSD. Use of the ANT could better target treatment and lead to future examination of attention treatment on neuroplasticity.

6. Research Plan:

This is a pilot study to test the effect of GMT plus Attention Training for Veterans with chronic mTBI. The research design is a parallel study with randomization to treatment or control with test administration at pre/post and six months following treatment.

Patients for the treatment and control group: participants that meet the inclusion criteria and exclusion criteria will be scheduled for a session to consent and begin screening tests to determine inclusion criteria #4 and exclusion criteria #4 and #5.

We will recruit 50 Veterans for the study (25 treatment; 25 control) and 50 informants:

1. all Veterans who have served in OIF-OEF-OND (Operation Iraqi Freedom-Operation Enduring Freedom-Operation New Dawn) with single- (at least brief loss of conscious) or multiple (with at least alteration of consciousness) mild traumatic brain injury (mTBI) during deployment, who seek services at North Florida/South Georgia Veterans Health System (NF-VHS).
2. TBI must have suffered their injury at least 6 months prior to study enrollment and currently be in stable neurological condition.
3. age range 18-55 years to reduce the impact of aging on treatment improvement.
4. Attention deficit of ≥ 1.5 SD below the mean of the Repeatable Battery for the Assessment of Neuropsychological Status attention index. This will ensure that participants have an objective attention deficit.
5. Family member or friend that is willing to complete the BRIEF-A (BRIEF-A guidelines of face-to-face interaction with the participant at least twice a week) at all measurement timepoints.
6. Access to a home computer, or smartphone with internet access.

Classification of Mild TBI severity will be determined from the Ohio State University TBI Identification Short-Form, and the updated 2015 VA/DoD classification detailed below in Table 1 for the mild criteria:

Table 1. Classification of TBI Severity (If a patient meets criteria in more than one category of severity, the higher severity level is assigned)

Criteria	Mild	Moderate	Severe
Structural imaging	Normal	Normal or abnormal	Normal or abnormal
Loss of Consciousness (LOC)	0-30 min	>30 min and <24 hours	>24 hours
Alteration of consciousness/ mental state (AOC)	up to 24 hours	>24 hours; severity based on other criteria	
Posttraumatic amnesia (PTA)	0-1 day	>1 and <7 days	>7 days
Glasgow Coma Scale (GCS) (best available score in first 24 hours)	13-15	9-12	<9

Patients for the treatment and control group will be excluded if:

1. History of pre-morbid learning disability
2. History of psychiatric diagnosis sufficiently severe to have resulted in inpatient hospitalization.
3. Neurological disease unrelated to TBI (seizure disorder, stroke)
4. Score < 90 on National Adult Reading Test (NART)

5. Failure of validity testing on the Test of Memory Malingering (TOMM). Score of 45 or less on TOMM Trial 2 or retention trial.
6. Reported alcohol or substance abuse within the past year
7. Reported involvement in current litigation
8. Recent change of medications for seizures, depression or memory.
9. Currently enrolled in other cognitive therapy that cannot be discontinued
10. Does not speak English fluently
11. Not competent to provide consent (also, not able to demonstrate understanding of expectations of study and potential risks of participation).
12. Uncontrolled, acute medical or psychiatric condition as indicated by the participant or observed by the research team member that would make it unsafe to participate in the research activities, i.e., precautions for active homicidal/suicidal intent, active psychosis, or acute symptoms requiring immediate medical attention.
13. Psychotropic drugs that have changed within the past two-weeks that would impact performance during assessment.

Informants will be enrolled if selected as a person to complete a questionnaire by the patient who observes their functional behavior at least two-three times a week and is at least 18 years old.

Protection of Data:

Datasets will be de-identified; participants will not be identified by name and data will be kept separate from test responses. Data will be entered into electronic databases that will include a study ID (not personal identifying information) and saved in a VA secured shared folder with access limited to research team members. Data from the Smartphone AP will be transferred via MyHealtheVet secure messaging which is compliant with all information security requirements with encryption from end-to-end. Participants' study records will not be released without written permission from the participant. Records of participants will be kept in locked file cabinets in a locked room. Access to those files will be restricted to authorized study personnel.

Recruitment: Patients from the BRRC recruitment data base will be contacted; clinicians will hand out fliers in North Florida/South Georgia Veterans Health Administration outpatient clinics; letters to inform Veterans with mTBI diagnoses of the study will be mailed; and fliers will be distributed to local Veterans groups and Veteran support centers at community colleges and universities. The proposed study has an existing approved protocol and patients are recruited through a variety of proven methods: patients from the BRRC recruitment data base will be contacted; clinicians will hand out fliers in North Florida/South Georgia Veterans Health Administration outpatient clinics; letters to inform Veterans with mTBI diagnoses of the study will be mailed; and fliers will be distributed to local Veterans groups and Veteran support centers at community colleges and universities.

Interested participants will be scheduled for an appointment to determine eligibility criteria. Once potential participants are deemed eligible, written informed consent will be obtained from each subject by the PI or trained research assistant. The PI or trained research assistant will explain the purpose of the project and describe the procedures to be followed. Participants will be asked to sign an informed consent after the purpose of the project, risks, and benefits have been fully explained in language a layperson can understand.

Participants can choose to participate in GMT or individual cognitive treatment as part of clinical care if they do not wish to participate in research.

Once the participant signs consent, any treatment with the investigators will be discontinued until the follow-up testing has been completed.

Once Veteran meets inclusion criteria, they will identify an informant that observes their functional behavior at least 2-3 times a week. The informant will be scheduled for an appointment for consent and to complete the BRIEF-A questionnaire. They will receive a phone call once a week to answer whether the homework was easy or difficult for the Veteran and see if there are specific cognitive issues that need to be addressed.

Due to the COVID 19 outbreak, this protocol has been modified to reduce the participants' risk of contracting COVID-19 from in-person exposure during treatment. GMT and attention training will be conducted by Telehealth using the VA Video Connect (VVC) service.

Randomization Procedure: 25 of the Veterans will be randomized to treatment while 25 will engage in BHW/movies as control participants. The Pocock-Simon covariate adaptive randomization procedure will be used so that, for each PTSD severity category, approximately 50% (25/25) of Veterans are assigned to treatment group; consequently, there will be approximately equal proportion of PTSD participants assigned to the treatment and control groups.

Each group of the 25 treatment and 25 control participants will also be randomized to training to complete the Test of Grocery Shopping skills in a virtual setting (V-Mart) during session 7 or 8.

Intervention

GMT: is a 10-session intervention to improve planning and problem solving. Interactive Power Point modules are administered by a cognitive therapist. Each session builds on the steps of a five-stage planning and problem-solving strategy. Veterans will be taught to generate and verbalize the following five-steps: “stop-what am I doing?”, “define the goal”, “list the steps”, “learn the steps”; then, “check-am I doing what I planned?” The five-stage strategy is then incorporated into a variety of activities in the laboratory and in-home assignments. At each session, the participant discusses utilization of the strategies in daily life and reviews progress. The following steps are taught during simulated tasks: 1) Identify Main Goal; 2) Break down task into sub-goals and steps for each goal; 3) List supplies needed; 4) Recognize potential barriers to completing goal; 5) Determine strategy to accomplish task: 6) Prepare to begin task with “presence of mind” exercise; 7) State goal out loud; 8) Begin task and stop self frequently to state main goal out loud and check to be sure one is working toward the goal (on target).

Generalization of laboratory practice to home environment is of critical importance. Unfortunately, the original GMT did not provide a method to monitor the frequency or success of home practice, nor a method to support productive practice in the home environment. In our prior work, we developed The Veteran’s Task Manager (A Smartphone application (AP)), which was specifically developed to utilize the strategies taught in the lab during GMT, support the home practice mandated by GMT, and monitor practice. Participants will use the AP features to break down tasks, estimate time to complete, check off each step as completed, respond to the visual/vibrating alert of “Goal” and respond to alert if “On Target”. Information will be collected by the AP, such as accuracy of planned steps, time to complete task, and number of distractions from goal. The AP will record the participant’s performance in functional practice at home and this information will be reviewed at the next lab session and recorded.

Attention Training: Veterans will also engage in BrainHQ™ attention training at home for one-hour, five days/ week comprised of selected components of BrainHQ from Posit Science Corporation (Table1). Once a week the Veteran will review and engage in Brain HQ with the therapist during a second two-hour weekly tele-health session. This web-based computerized CRT modality of cognitive training is a restorative or "bottom-up" approach that targets basic cognitive skills such as arousal and vigilance processes, attention and information processing, and directly engages fundamental attention-control skills through repetitive graded exercises. BrainHQ is software designed such that the speed and complexity of exercises increase as the user's performance improves to consistently maintain a high proportion of successful trials while gradually increasing task demands. BrainHQ has been designed as a web-based platform, and participants can perform tasks at home on their own home computers. Veterans will be given a code and password from the research staff to sign into Brain HQ so that their personal information is not recorded. Speed and accuracy as well as time spent engaged are downloaded directly from the Brain HQ website by the research staff. Only the PI will have the key to code names to identify the link to the Veteran. Therapist and Veteran will identify functional activities in the home that require attention skills and homework will be assigned to practice functional tasks to complete using Veterans Tasks Manager Smartphone AP and the Goal Attainment Scale.

Table 1. Selected BrainHQ™ Tasks

BrainHQ™ Task	Cognitive Domain Trained
"Divided Attention"	Divided attention
"Target Tracker"	Divided attention
"Double Decision"	Useful field of view &visual processing speed
"Mixed Signals"	Selective attention
"Freeze Frame"	Alertness

Control Group: Participants that are randomized to this group will provide a control for repeat testing and will provide similar characteristics with the treatment group, such as severity of PTSD. To equate for time and exposure to therapist, the participants will engage in a Brain Health Workshop (BHW) and watch geographic movies. BHW was developed specifically for consistency with GMT session length and contact with the facilitator[49]. BHW is an education presentation on brain function and cognitive principles of learning with homework (readings assigned) and quizzes on information covered. To match time and contact of attention training, control participants will meet with the therapist for a separate two-hour session from BHW and watch geographic movies followed by a short quiz. This will equate the amount of time and contact experienced by the treatment group for both the GMT and attention training sessions.

Measurement: Veterans with mTBI will qualify for the study if they demonstrate a deficit in attention as measured by formal neuropsychological testing and pass effort testing. The following measures (Table 2) will be administered at week 1 (before intervention), week 11 (after intervention) and at week 36 (six months after intervention). The primary outcome measures for Aim 1, will be the computerized Tower of London (cTOL)[38] and the Test of Grocery Shopping Skills (TOGGS).

The following measures will be administered by an email link from the University of Florida REDCap application: Combat Exposure Scale, Neurobehavioral Symptom Inventory, Beck Depression Inventory, Alcoholic Use Disorders Identification Test, PTSD Checklist for DSM5, Brief Pain Inventory, Behavioral Rating Inventory of Executive Function for Adults, and State Trait Anger Expression Inventory.

	Table 2. Study Measures		
Domain	**Purpose**	**Administration session**	**Measure(s)/Minutes to Administer**
	Pre-Treatment Screening/Assessment		
Attention	Attention impairment	Weeks	RBANSAttention index
Effort	Determination of potential suboptimal effort	1	*TOMM/5
Word-reading	For group matching—estimation of pre-morbid cognitive ability	1	*NAART/10
	Primary Outcome Measures		
Executive Function	Assesses problem-solving, planning and attention	1, 11, 36	cTOL/20
Functional	Assess performance of a complex task	1, 11, 36 7 or 8	ToGSS,/30 V-Mart/20
	Secondary Outcome Measures – Cognition		
Attention	Behavioral performance associated with dissociable attention networks—alerting, orienting, executive control	1, 11, 36	ANT/ 20
Social Role Participation	Evaluate involvement and participation in life situations	1, 11, 36	CRIS/5
	Tertiary Outcome Measures		
Moderating Variables	PTSD symptoms, pain, history of substance abuse, Depression, number of concussions, combat exposure, anxiety, fatigue, sleep.	1, 11, 36	*PCL-5/ 5, BPI/ 2, *AUDIT-C/2, *BDI-II/ 5, *OSU-TBI/5, *CES/ 5, *NSI/ 5, *STAXI-2/5, *MFIS/3, *PSQI/5
Cognition	Overall cognitive function	1, 11, 36	RBANS/20
Executive function	Secondary measure of executive function, attention and symptom reporting	1, 11, 36	EXAMINER/ 30, *BRIEF-A (self and informant report)/10
Functional Tasks	Attaining functional goals in attention and executive function	7 or 8	GAS/5, VTM-APP/task dependent
Usability	Evaluate user satisfaction of GMT, APT-III, Brain HQ and VTM-APP	11	TSQ/ 2
Usability	Patient logs sleep/wake times	1, 11, 36	CSL/2
Total Administration Time			Session 1: 179 minutes or 3 hours
	Abbreviations: Attention Network Task (ANT); Alcohol Use Disorders Inventory (AUDIT-C); Beck's Depression Inventory (BDI-II); Brief Pain Inventory Short Form (BPI); Behavior Rating Inventory of Executive Function-Adult (BRIEF-A); Combat Exposure Scale (CES); Community Reintegration in Service members (CRIS); Consensus Sleep Log (CSL); computerized Tower of London (cTOL); Executive Abilities: Measures and Instrument for Neurobehavioral Evaluation and Research (EXAMINER; an NIH Toolbox measure); Goal Attainment Scale (GAS); Modified Fatigue Impact Scale (MFIS), Neurobehavioral Symptom Inventory (NSI); North American Adult Reading Test (NAART); Ohio State University-TBI identification Method (OSU-TBI); Pittsburgh Sleep Quality Index (PSQI); Post Traumatic Stress Disorder Checklist (PCL-5); Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); State Trait Anger Inventory (STAXI); Test of Grocery Shopping Skills (ToGSS); Test of Memory Malingering (TOMM); Technology Satisfaction Questionnaire (TSQ); Virtual Reality Market (V-Mart); Veteran's Task Manager Smartphone Application (VTM-APP). *Common Data Element measures.		

Description of Measures

1. Screening Measures:

National Adult Reading Test (NART) is an oral reading test consisting of 50 words (Nelson and Willison, 1991). The NART can be used to estimate premorbid intelligence and will be used as a screen. Similar to Levine et al. (2007), we will use the cut off score of > 90 as an inclusion criterion to ensure that frontal lobe impairment is not the result of low premorbid intelligence, and that the subject will be able to read the material during treatment.

Test of Memory Malingering *(*TOMM*):* is frequently used to detect poor effort on neuropsychological assessment and has been validated with TBI patients (Tombaugh, 1996; Slick et al., 2004; DeBoar, 2007). This test will be used to screen out patients scoring 45 or below on Trial 2 or the Retention Trial (Trial 1 scores will not be used) to provide a level of confidence to the results of outcome measures.

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS*):* is a cognitive screening instrument The RBANS is composed of 12 subtests that yield 5 index scores and a total score. The subtests of List Learning and Story Memory comprise the Immediate Memory Index; Figure Copy and Line Orientation yield the Visuospatial/Constructional Index; Picture Naming and Semantic Fluency yield the Language Index; and Digit Span and Coding comprise the Attention Index. Four subtests make up the Delayed Memory Index, specifically, List Recall, List Recognition, Story Recall, and Figure Recall (Randolph, Tierney, Mohr, & Chase, 1998). Administration is approximately 20 minutes and has been used to assess cognition in mTBI (Cooper et al., 2010). An attention score of 1.5 SD below the mean will be used to include participants with an attention deficit. The index scores of the RBANS will also be used to characterize the patient's cognitive capacity and to determine whether aspects of cognitive ability impact response to treatment.

2. Primary Treatment Outcome Measures:

Tower of London (TOL): is a computerized program in which patients are shown two pictures simultaneously of a goal board and a test board (Unterrainer et al, 2006). Each picture shows three balls of different colors arranged on three pegs, with the balls in a unique arrangement in each picture. Patients are instructed to determine the fewest possible moves of the balls in the test picture to make the arrangement of balls identical to that of the goal picture within 60 seconds. The screen reports whether the response is correct or incorrect. Test administration is less than 30 minutes for each session (pre/post/follow-up). Each set consists of 30 problems of variable difficulty, determined by variables, such as, the number of moves needed to solve the problem (Berg and Byrd, 2002). In turn, each set consists of the same number of 4, 5, 6 or 7 move problems and has the same average difficulty level. Difficulty rating is based on global and specific problem parameters shown to affect the planning process (Kaller, 2007, 2008, 2009; Berg, Byrd, McNamara, & Case, 2010; Kaller, Unterrainer, Rahm, & Halsband, 2004). The dependent variables are the total time spent solving the problem and the optimal moves made toward the goal display. Based on our previous studies, executive function represents three factors (behavior regulation, emotional regulation and metacognition) (Waid, Wen, Heaton, and Velozo, submitted to Neuropsychology). GMT is a metacognitive training with emphasis on planning prior to engaging in a complex task. Therefore, a primary measure that captures the planning and problem solving of a multi-step task, called the Tower of

London (TOL), was selected. Based on results from our preliminary study, the dependent variables of total time and optimal moves will be used to determine treatment effect. While not all of the participants in our previous work demonstrated significant improvement on these variables, group differences based on paired T-tests were significant in Total Time (p=0.026) and Optimal Moves (p=0.022) from baseline to treatment. In addition to our findings, Levine (2011) demonstrated a significant change in the TOL following GMT for a mixed neurological sample compared to a control group. Thus, the TOL appears to be sensitive to the effects of GMT and will be compared from post and 6-month follow-up to screening to determine treatment gains (HO#1).

Test of Grocery Shopping Skills (TOGSS): is a performance-based measure of a person's ability to locate items in an actual grocery store. In addition to measuring specific grocery shopping skills, TOGSS scores are associated with cognitive abilities, particularly executive functioning (Rempfer, Hamera, Brown, & Cromwell, 2003; Zayat, 2006). TOGSS administration is 20-30 minutes. The examinee is shown a grocery list of 10 specific items and asked to locate the lowest priced brand for each one. Outcome variables (accuracy, speed and efficiency) will be tested to determine improvement in functional performance (HO#2). Veterans will have the option of practicing shopping in a virtual grocery store displayed on a monitor using a game controller to navigate prior to completing the TOGGS in an actual grocery store. Both the Veteran and the clinician will identify barriers to efficient shopping and will plan strategies to overcome barriers.

3. Secondary Measures:

Attention Network Task (ANT): presents participants with a target item (>) on a computer screen surrounded by congruent (> > > > >), neutral (- - > - -), or incongruent flanker stimuli. Stimulus presentation is preceded by different cue conditions and the participant is instructed to identify the target stimulus and respond by selecting 1 or 5 on the computer keyboard. To characterize the type of attention deficits of each participant, we will use the attention network task (ANT) to determine the relationship with the alerting, orienting and executive aspects of attention to treatment effects. Given the success of the ANT in discriminating impairment among the three attentional networks in Veterans with mTBI and PTSD, we will utilize this method to study differential response of attention networks to cognitive remediation (Ho #1, secondary measure).

Community Reintegration of Service Members (CRIS): will be used to measure participation. The CRIS was developed specifically for soldiers with disabilities (Resnik et al., 2009, 2011) and is available in two formats, a paper and pencil version with 128 items and a computer adapted version that takes no more than 10 minutes to complete. Three scales are found in the CRIS and have good internal reliability: Extent of Participation = 0.91, Perceived Limitations = 0.93, and Satisfaction with Participation = 0.97 (Resnik et al, 2009). Meaningful detectable change indices were 5.9, 6.2, and 3.6, respectively for Extent, Perceived and Satisfaction subscales (Resinik et al, 2012). CRIS-CAT scores were predictive of SF-12 physical and mental health related quality of life scores at the 1-year follow-up (Resinik et al, 2012). Preliminary analysis described reveals good internal reliability and separation into ability levels in a sample of 44 mTBI Veterans. Test-Retest reliability is 0.95 for Extent of participation; 0.85 for Perceive limitation; and 0.95 for Satisfaction scales (Ho#2, secondary measure).

4. Tertiary Analysis Measures for Moderator Variables or to Characterize Participants

Post-Traumatic Stress Disorder (PTSD) symptom checklist-5 (PCL-5): The PCL-5 is a 20-item self-report measure that assesses the 20 DSM-5 symptoms of PTSD. The PCL-5 has a variety of purposes, including: 1. Monitoring symptom change during and after treatment 2. Screening individuals for PTSD 3. Making a provisional PTSD diagnosis. The PCL-5 will be used to determine the impact of PTSD on the response to treatment.

Brief Pain Inventory (BPI) is a 9-item self-administered questionnaire used to evaluate the severity of a patient's pain and the impact of this pain on the patient's daily functioning. The patient is asked to rate their worst, least, average, and current pain intensity, list current treatments and their perceived effectiveness, and rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life on a 10-point scale. The BPI-sf is a modification of the Brief Pain Inventory - Long Form, which includes additional questions on demographics (date of birth, marital status, education, employment), pain history, aggravating and easing factors, treatment and medication, pain quality, and response to treatment.

Alcohol Use Disorders Identification Test (AUDIT-C) asks 3 questions on the quantity and consequences of alcohol use with a five-option rating of never to 4 or more times a week. The AUDIT will be used to determine the impact of alcohol use on the response to treatment.

Beck Depression Inventory (BDI-II): is a 21-item questionnaire filled out by the individual diagnosed with TBI in the presence of the Principal Investigator. Questions are rated using a 4-point scale and cover symptoms of depression such as hopelessness, irritability, guilt, fatigue, weight loss and lack of interest in sex. The reliability of the BDI in TBI has been reported at .92 (Green, 2001; Beck et al, 1996).

Combat Exposure Scale (CES) is 7-item self-report measure that determines wartime stressors exhibited by combatants. Individuals are asked to respond based on their exposure to various combat engagements, such as firing rounds at the enemy and being on dangerous duty.

Neurobehavioral Symptom Inventory (NSI) is a 22-item self-report questionnaire developed by Cicerone and Kalmar (1995) to assess post-concussion symptoms after mild traumatic brain injury.

State-Trait-Anger-Expression-Inventory (STAXI) is a self-report questionnaire measure that focuses on anger expression. It assesses both the current (or state) anger of the applicant, and the generally characteristic (trait) anger level.

Modified Fatigue Impact Scale (MFIS) is a modified form of the Fatigue Impact Scale (Fisk et al, 1994b) based on items derived from interviews with MS patients concerning how fatigue impacts their lives. This instrument provides an assessment of the effects of fatigue in terms of physical, cognitive, and psychosocial functioning.

Pittsburgh Sleep Quality Index (PSQI): is a 19-item self-rated questionnaire for evaluating subjective sleep quality over the previous month. Seven component scores are added to obtain a global score ranging from 0–21, with higher scores indicating worse sleep quality. The PSQI has a sensitivity of 89.6% and specificity of 86.5% for identifying cases with sleep disorder and has been used in a wide range of population-based and clinical studies. Since sleep disturbances are common complaints for Veterans returning from deployment and has been known to impair cognition, the PSQI will be used to determine whether sleep disturbances interfere with treatment response.

EXAMINER: A battery of 10 executive function tasks have developed by a NINDS funded project to use in clinical research studies. The tasks take approximately 60 minutes to administer via a computer and result in 12 primary variables. Tasks include: Dot counting (count blue dotes on a series of screens and recall the number of dots across screens), N-back (identify whether a series of locations match the location presented 1 or 2 before), Flanker (indicate the direction of an arrow that is flanked by arrows pointing in the opposite direction), Continuous Performance Test (respond to certain stimuli and withhold response to other stimuli on a computer screen), Anti-saccades (move eyes toward a stimulus and moves eyes away from a stimulus), Set-shifting (switch between a homogeneous matching task and a heterogeneous matching task), Phonemic Fluency (name as many words as possible with the same letter), Category Fluency (name as many items as possible in a category), Unstructured Task (complete puzzles within 6 minutes with the goal of earning as many points as possible), and the Social Norms Questionnaire (answer yes no questions about socially appropriate behaviors). Test re-test reliability is .94 and correlated with the FrsBe -0.57 in a multi-neurologic population.

Behavior Rating Inventory of Executive Functions–Adult (BRIEF-A) is a self and informant report questionnaire consisting of 75 statements about executive behaviors. There are three possible responses to items: often, sometimes, never. There are nine subscales: inhibit, self-monitor, plan/organize, shift initiation, task monitor, emotional control, working memory, and organization of materials. Normative self-report (n=1,050) reliability ranges from .73 to .90 for the scales and .93 to .96 for Index and Global Executive Composite scores. While the reliability in a mixed clinical sample (n=233) ranged from .80 to .94 for scales and .96 to .98 for Index and Global Executive Composite scores. Test-retest reliability over 4 weeks averaged .82 to .93 on the scales and .94 for Index and Global Executive Composite scores. The total BRIEF-A score correlates at .84 with the Dysexecutive Questionnaire (Roth, 2005). In a sample of patients diagnosed with TBI, the MI reported a cronbach alpha of 0.96 (Waid-Ebbs et al., 2012). The Metacognitive Index score of the BRIEF-A will be used to detect generalization of treatment effect and impact of specific executive function deficits on treatment gain.

Goal Attainment Scale (GAS) is an individualized outcome measure involving goal selection and a five-point goal scaling that is standardized in order to calculate the extent to which a patient's goals are met. The patient and therapist write goals specific to the patient's needs, such as: +2 able to find 4-5 items; +1 able to find 3 items; 0 able to find 2 items; -1 able to find 1/5 items; -2 unable to stay in store and locate items.

Veteran's Task Manager Smartphone Application (VTM) is a free Smartphone application (AP) specifically developed to utilize the strategies taught in GMT will be loaded from the Apple store or Google store by the participant to their Smartphone (iPhone or Android). Participants will use the application features to break down tasks, estimate time to complete, check off each step as completed, respond to visual/vibrating alert of "Goal" and respond to alert if "On Target". Information, such as accuracy of planned steps, time to complete task, and number of distractions from goal will be collected by the AP. Data will only be transferred via secure messaging in MyHealtheVet or shown to the therapist during an individual session

Technology Satisfaction Questionnaire (TSQ) is a questionnaire used to capture satisfaction level for each technological measure used (e.g., GMT, BrainHQ, APT-III, and VTM-APP).

Consensus Sleep Log (CSL) is a measure that patient uses to log sleep/wake times over a one-week period.

Demographics will be collected using the Federal Interagency Traumatic Brain Injury Research forms, including amount and type of productivity (work and unpaid volunteer). Details of TBI events and history will be documented using the Ohio State TBI identification Method which is a standardized procedure for eliciting a person's lifetime history of TBI via a 3-5-minute structured interview.

Statistical Analysis Plan

Aim 1: Determine the treatment effect of attention training combined with GMT in Veterans with mTBI. Hypothesis 1a: GMT plus attention training will significantly improve performance on tests of cognition compared to the control group. 1b: Treatment gains will translate to functional activities compared to controls.

For both Hypothesis 1 and 2: A multiple linear regression model will be used to determine if there is a significant difference between the treatment and control groups in tests of cognition and function. Separate models will be fit for each outcome measure (cTOL, ANT, TOGSS, CRIS) the baseline measure and treatment group indicator will be used as covariates in the model. The Wald test will be used to determine if the coefficient for treatment group is significantly different from zero, indicating a significant treatment effect. Effect sizes for between-group differences will be estimated using the coefficient of the group indicator in the model.

Tertiary analysis: Other moderator variables (Table 2) will be examined to determine whether a linear relationship exists between changes in problem solving, attention or participation. These variables include PCL-5 total score and index scores (such as intrusions), BPI total score, AUDIT-C total score, BDI-II total score, number of concussions, STAXI-2, PSQI, MFIS and CES total score.

Sample Size: A sample size of 50 participants equally randomized into treatment or control groups will yield 80% power to detect an effect size of 0.81[39]. In other words, if the true improvement in the treatment group is 0.81 standard deviations greater than the control group, then the pilot study has an 80% chance of detecting a significant difference. Based on our preliminary analysis of 14 GMT and 3 BHW controls, we estimate a large effect size of 1.76 (3.16, 0.37) for the cTOL time to first move, a moderate effect size of 0.827 (-0.46, 2.10) for cTOL optimal moves, and a moderate effect size of 0.67 (-0.60, 1.95) for cTOL time to completion[40].

7. Possible Discomforts and Risks:

The primary hazard to participation in the experimental/clinical neuropsychological measures and interventions is fatigue/frustration. Examiners are trained to respond to such reactions and provide encouragement, breaks, and assistance as needed. Testing or training will be terminated, and the Veteran will be debriefed, in the event of adverse emotional reactions or extreme fatigue, which are very rare. In the event that the participant answers 3 on question 9 of the Beck Depression Inventory (depression questionnaire used during screening) or actively expresses thoughts of harming themselves, the Veterans Crisis Line (also called the National Suicide Prevention Lifeline 800.273.8255 press 1 for Veterans Crisis Line) will be called by the research team. This will be performed prior to the subject leaving the sight of the study staff.

8. Possible Benefits:

The proposed project has the potential to provide information that will enable clinicians to target Veterans with disrupted attention neural networks with effective treatments specifically prescribed to a particular component of attention. This will benefit Veterans by improving specific attention components that in turn improve other cognitive processes. The potential benefits far outweigh the minimal risks. Veterans will be reimbursed for each session of their participation.

9. Conflict of Interest:

Dr. Waid-Ebbs and Dr. Perlstein have no conflict of interest to declare for this study.

10. Records Management:

The records will be retained and kept in accordance with the VA regulations.

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