Protocol **ID#: B0902**-W

1. **Project Title:** Metacognitive Training to Enhance Strategy Use In Blast-Related TBI

2. **Investigator(s):** PI: J. Kay Waid-Ebbs, PhD

3. **Abstract:**

Increasing numbers of veterans are experiencing executive dysfunction due to a mild traumatic brain injury (mTBI). Executive dysfunction interferes with participation in home and work activities. Therefore, an effective intervention is needed that will provide significant and long-lasting improvement in the everyday lives of our veterans. Goal Management Training (GMT), an intervention that teaches a five-step strategy to improve planning and organization, has demonstrated promising results (Levine et al., 2000; 2007). However, there are several weaknesses regarding validation of the GMT in individuals with TBI. Therefore, the proposed study is needed to determine the effect of the 10-session GMT on veterans with mTBI. This study will 1) administer the 10-session GMT to individuals that have an objective executive dysfunction; 2) due to mTBI; 3) use probes designed to measure the activities trained in GMT, along with a measure of generalization; and 4) determine the number of subjects needed to demonstrate a treatment effect in a future randomized clinical trial.

4. **Background:**

Brain Injury has become the signature wound of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF). An estimated 20,000 military personnel have been wounded in action primarily due to blasts (US, 2006). However, an even larger number are thought to have suffered a mild traumatic brain injury (mTBI) that was left undetected (Lew, 2005). A mTBI is diagnosed if any of three following criteria are met: 1) loss of consciousness less than 30 minutes with a Glasgow Coma Scale of 13 or above; 2) any loss of memory for events immediately before and after the event (not longer than 24 hours); any alteration of mental state at the time of accident; 3) any focal neurological deficits that may, or may not, be transient (ACRM, 1993). Of an at risk group evaluated at Walter Reed during 2003-2004 an estimated 59% suffered at least a mild TBI while in combat (Warden, 2005). It is known that over 2 million civilians sustain a TBI each year, of which an estimated 85% are mild (Sherer and Novack, 2003). However, this figure may be an underestimation, since some individuals that sustain a mild TBI do not seek treatment.

The problems that result from mTBI are diverse. During the acute stage individuals may experience obvious problems with attention, verbal retrieval, forgetfulness, headache, dizziness, irritability, drowsiness, sleep disturbances and fatigue (Ponsford, 2000). In addition, military personnel also suffer emotional issues such as PTSD, depression and anxiety disorders (Lew, 2005). While the majority of individuals with

mTBI are thought to totally recover within the first three months, several studies have found up to 48% continue to experience one or more symptoms up to a year after the injury (Alves, 1993; Jacobson, 1995). For example, Drake et al. (2000) found in a military sample that 46% were not able to return to their previous duty after three to fifteen months; with memory and executive functions impairments as the greatest risk factor.

The chaos and trauma that occur when an explosive device is detonated make it difficult to follow the diagnostic criteria outlined above. Even so, military personnel exposed to a blast may suffer a mild TBI because the brain is especially susceptible to the "blast over pressurization" that affects fluid filled organs of the body (Mayorga, 1997). Exposure to a blast may cause diffuse axonal damage, as well as damage sustained from being thrown or having objects hit the head (Lew, 2005). The frontal lobes are most susceptible to injury due to the contact of the bony orbital surface to the frontal lobes and the frontal poles (Damasio & Anderson, 2003). Therefore, the diffuse axonal damage and contusions will occur prominently in the frontal lobes as well as other cortical and subcortical structures, which is evident in the cognitive deficits following a mTBI.

Executive functions are most commonly affected by damage to the frontal lobes. They can be disrupted by damage to the focal areas in the frontal lobes or to the frontal-subcortical circuits that integrate cognitive, self-regulatory, and emotional behavior (Stuss, 2007). In fact, disorganization as a result of executive dysfunction is the most common complaint about individuals with TBI (Mateer, 1987). The self-regulation of behavior is less necessary in well-learned activities that become automatic but is more necessary in new activities that require inhibition of an over-learned plan so that a new problem-solving strategy can be developed. A new plan requires the ability to maintain intentions as well as the execution of those intentions (Levine, 2000). After frontal injury, intention and action can become dissociated; individuals with frontal lobe damage may be able to tell you the appropriate action to take, but do not follow that action (Luria, 1966). Several steps need to be coordinated for an individual to achieve his/her intentions. First the difference between the current state and the desired state must be detected. Second, the steps needed to reach that desired state must be formulated. Third, the desired state must be kept in mind while resisting other distractions. Fourth, the barriers that occur along the way must be overcome until finally the goal is achieved. Once the goal is achieved, the result must be evaluated. Duncan (1986) refers to the inability to complete step 3 as "goal neglect". In order to be able to live independently, we must be able to keep in mind what we are doing, avoid distractions, respond to novel problems in new ways while inhibiting the ineffective way we have responded in the past, and evaluate how well we did. Individuals with executive dysfunction will have difficulty performing the tasks necessary to deal with novel situations in an unstructured setting.

Given the numbers of military personnel who may be struggling with executive dysfunction, an effective intervention to improve executive functions is needed. However, there are no treatments for executive dysfunction in mTBI that have been rigorously investigated. Robertson (1996) developed a treatment package called goal management training (GMT) based on Duncan's theory of "goal neglect". GMT is a 7-session (2 hours/ session) interactive module that is presented in a group format. A 5-

stage strategy is taught to the participants and is then incorporated into tasks practiced in the group session as well as in tasks each participant is to practice at home. The 5-stage process consists of “stop-what am I doing”, “define the goal”, “list the steps”, “learn the steps”, then “check-am I doing what I planned”. Levine validated the GMT by randomly assigning 30 TBI patients to either a one-hour version of GMT or motor skills training (Levine et al. 2000). The one-hour GMT was associated with improvements (being more careful as demonstrated by taking longer to complete the task after training) in paper and pencil tasks (proof reading and grouping) that simulated tasks requiring cognitive control. Since then, Levine et al. have modified the GMT module and increased the length of training to seven, two-hour sessions (14 hours total) (Levine et al., 2007). To date the only published use of this expanded GMT has been with an elderly sample, embedded in a larger rehabilitation package. The expanded version (modified GMT) may offer promise to the mTBI population as well.

The proposed study is needed to determine the effect of the expanded GMT in veterans with mild TBI. 40-North Florida/South Georgia, Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) Veterans will be recruited who meet criteria for TBI (ARCM, 1993) and have current executive dysfunction.

Two screening measures, Delis-Kaplan Executive Function Test System (D-KEFS) color word interference test and the Stop Signal Task will be used to select individuals that demonstrate deficits in inhibition which is within the domain of executive function.

The Computerized Tower of London will be used to assess the improvement of inhibition as a result of the intervention. To measure the effect of the GMT on observations of executive functioning in the home environment (generalization) the Behavior Inventory of Executive Functioning in Adults (BRIEF-A) was selected. The BRIEF-A is a global measure of executive functioning and will demonstrate whether improvements in simulated tasks generalize to overall functioning as observed by a proxy in the home.

In addition to improved measures, the current 7-session/14-hour version of the GMT is the same as the one-hour version, however, the expanded version allows for additional practice of the learned strategies in both the group setting and in the home setting. The increased practice may decrease the effort needed to apply the strategies and increase the use of the strategies beyond the therapy sessions. In fact, Robey (1998) demonstrated that two or more hours of therapy a week produced a greater change than therapy delivered less than one and a half hours per week. Therefore, the expanded version is anticipated to show a stronger effect than the 1-hour GMT. Turner and Levine (2004) predicted that individuals with mild TBI would be able to apply the strategies learned in GMT easier than individuals with moderate or severe TBI. Therefore, it is expected that the proposed study will produce a magnified effect over the Levine et al. (2000) study by using improved measures, using a longer treatment of 20 hours instead of one hour, and applying the intervention to individuals with mild TBI versus moderate and severe TBI.

5. Specific Aims:

Specific Aims: The purpose of this Phase I study is to test an innovative treatment for executive dysfunction in veterans with mTBI that utilizes formalized and manualized procedures that can be exported for use in a subsequent randomized clinical trial.

Aim 1.

Aim 1 is to test the benefits of GMT for improving executive function.

Hypothesis 1a: GMT will significantly improve problem solving ability compared to the control group (primary measure: time to completion on the Tower of London (cTOL). Since PTSD is prevalent and a potentially influencing co-morbidity, we will to investigate whether there is a significant interaction between treatment group and PTSD severity. Secondary measures include number of optimal moves on the TOL; and measures derived from the Stop Signal Task (SST; a measure of inhibition control).

Exploratory Hypothesis 1.a.GMT will significantly improve everyday activities that require executive function skills (primary measure: Behavior Rating Inventory of Executive Function-Adult version, secondary measure: CRIS).

Analysis Plan for Hypothesis 1. and Hypothesis 1.a. To test the first specific aim (hypothesis 1), the primary analysis will use two sample t-test to compare group A (intervention) and group B (control) on improvements in time to completion on the TOL. In addition, as an exploratory analysis, we will perform a regression analysis that includes treatment group, PTSD severity and their interaction as independent variables, to adjust for PTSD severity and to investigate whether there is interaction between treatment group and PTSD severity. Similar analyses will be performed for hypothesis 1 for secondary outcome variables of change in index of optimal moves on the TOL and reaction time (RT) and accuracy on SST. To test hypothesis 1a, exploratory *tertiary analysis* using paired t-tests will determine whether treatment effect generalizes to executive function performance in everyday activities (BRIEF-A) or engagement in community participation (CRIS).

Aim 2

Aim 2 is to investigate factors which affect response to treatment.

Hypothesis 2. Baseline cognitive ability, depression, sleep, and presence of PTSD will have a significant effect on response to treatment.

Analysis Plan for Hypotheses 2. To test the second specific aim, a general linear regression will be used to determine whether any of the four factors is associated with response to treatment. The analysis will be restricted to the participants assigned to the intervention group. The dependent variable for the regression model will be 'time to completion' on the TOL, and the independent variables will be CWI, BDI-II, PCL-M and PSQI scores.

6. Research Plan:

To determine the effect of GMT on veterans with mTBI the following research will be conducted. Clinical staff from the NF/SG VHS will hand out recruitment flyers or refer OEF/OIF/ONF veterans diagnosed with mTBI to the Principal Investigator. Referred Veterans will be contacted by the PI or interested Veterans will contact the PI. Veterans that meet the inclusion/exclusion criteria will be scheduled to obtain consent. Once

consent has been obtained the veteran will be scheduled for the first screening visit. Veterans that meet inclusion criteria will be randomly assigned to either treatment or control groups, in a ratio of 38:16. In addition, the Pocock-Simon covariate adaptive randomization procedure will be used so that, for each PTSD severity category within each of the two sites, approximately 70% (38/54) of subjects are assigned to treatment group; consequently, there will be approximately equal proportion of PTSD subjects assigned to the treatment and control groups within each of the two study sites.
Each veteran will complete testing prior to a 10-week intervention or control period; after intervention or control period; and at a one-month follow-up. Intervention will be offered to participants in the control group once testing is complete.

Participants will also be recruited and run in a parallel study in Durham under a Durham VA IRB approval. A total of 168 participants are anticipated to be enrolled in both Gainesville and Durham. Data from Durham will be entered in a VA share drive that both Gainesville and Durham staff can access. Data will not be transferred.

Table # 2 Study Design

	1st Measure	GMT/Wait	2nd Measure	3rd Measure
Group A **(n=38)**	Pre-treatment testing	**GMT/FP** 10 wks	Post-treatment testing	Follow-up testing
Group B **(n=16)**	Pre-Control testing	**Control (Brain Health Workshop)** 10 wks	Post-control testing	Follow-up Control testing

Methods

Subjects

Proxy/Informant: patient will select a person to answer a questionnaire on their executive function that observes the patient at least 2-3 times a week and is at least 18 years of age.

Patient Inclusion Criteria:

- Diagnosis of Mild TBI or concussion by a physician or neuropsychologist in the medical record compliant with the American Congress of Rehabilitation Medicine; any of three following criteria are met: 1) loss of consciousness less than 30 minutes with a Glasgow Coma Scale of 13 or above; 2) any loss of memory for events immediately before and after the event (not longer than 24 hours); any alteration of mental state at the time of accident; 3) any focal neurological deficits that may, or may not, be transient (ACRM, 1993).
- Executive dysfunction determined by at least 1.5 standard deviation below the average scaled score (corrected for age) on either the Delis-Kaplan Executive function System (D-Kefs) Color Word Interference Test, or the EXAMINER flanker task.
- Age 18 to 55 years
- At least 4 months post injury
- Family member or friend that is willing to provide feedback

Exclusion Criteria:

- History of pre-morbid learning disability
- History of psychiatric diagnosis sufficiently severe to have resulted in inpatient hospitalization.
- Neurological disease unrelated to TBI (seizure disorder, stroke, ADHD)
- Score < 90 on National Adult Reading Test (NART)
- Failure of validity testing on either the Test of Memory Malingering (TOMM),). Score of 45 or less on TOMM Trial 2 or retention trial.
- Reported alcohol or substance abuse within the past year
- Reported involvement in current litigation
- Recent change of medications for seizures, depression or memory.
- Currently enrolled in other cognitive therapy that cannot be discontinued
- Does not speak English fluently
- Not competent to provide consent (also, not able to demonstrate understanding of expectations of study and potential risks of participation).

Procedures

Intervention: The GMT is a 7-session intervention has been modified to a 10-session (2 hours/ session) interactive Power Point module that is presented in an individual or group format. Sessions 5, 6 and 7 have been split into two sessions each with time added to set-up and review functional practice. If a group format, the subject will be incorporated into a therapy session with 3-5 other participants (either other clinical patients or research participants diagnosed with TBI). During each session, a 5-stage strategy is taught to the participants. The 5-stage process consists of “stop-what am I doing?”, “define the goal”, “list the steps”, “learn the steps” then “check-am I doing what I planned”. The strategy is then incorporated into tasks practiced in the group session as well as in tasks each participant is to practice at home. The participants discuss utilization of the strategies and support the other members in the group. Friends or family members will participate in a training session prior to beginning GMT with the subject. The family member will be called each week during the GMT and asked to report whether the subject had an easy or difficulty time completing the homework assignments each week.

Simulated Practice In The Laboratory: Tasks during GMT training include exercises such as: 1) clapping to words while inhibiting clapping to a targeted word; 2) card sorting; 3) decision making and planning in order to complete five activities within a four minute time span; 4) Catalog Task; and 5) Book keeping task. The exercises start with relatively easy tasks and progress to more complex tasks. Participant’s strengths and weaknesses are discussed. Improvements are identified and reinforced as they learn more efficient planning and problem solving. 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 mindedness” 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).

Functional Practice with Smartphone Technology: In addition to GMT in the lab, three tasks will be first practice in the lab, than practiced at home. Participants will

select from the following: meal planning and shopping; planning a party; building a birdhouse; or paying monthly bills. A Smartphone application (AP) specifically developed to utilize the strategies taught in GMT will be loaded onto the participant's Smartphone (iPhone, iTouch, or Droid). Veterans that do not already possess one of the devices will receive one as part of their clinical service through prosthetics. Training will begin during the first session to learn the features of the technology they will need (calendar, list, alarms) using Michelle Wild's standardized learning procedure outlined in her guide books (http://pda4memory.com) that have been designed to train individuals with TBI how to use Smartphones. 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 not be electronically transferred; the participant's performance in functional practice at home will be reviewed and documented at the next lab session.

Control Group Intervention. The Brain Health Workshop (BHW; Levine 2011) was developed specifically for consistency with GMT session length and contact with the facilitator (Levine, 2011). BHW is an education presentation on brain function and cognitive principles of learning. Information about stress reduction, sleep hygiene, energy management, exercise and communication are covered, with homework and quizzes on information covered.

Table 1: Testing Schedule

Screening	Pre-Treatment	Post Treatment #	One-Month f/u#
D-KEFs Color-Word Interference Test		**D-KEFs Color-Word Interference Test**	**D-KEFs Color-Word Interference Test**
NART	***BRIEF-A**	***BRIEF-A**	***BRIEF-A**
TOMM	**PSQI**	**PSQI**	**PSQI**
	Tower of London	**Tower of London**	**Tower of London**
EXAMINER	**EXAMINER**	**EXAMINER**	**EXAMINER**
PCL-M	**RBANS**	**RBANS**	**RBANS**
	Stop-Signal Task	**Stop-Signal Task**	**Stop-Signal Task**
	Beck Depression Inventory-II	**Beck Depression Inventory-II**	**Beck Depression Inventory-II**
	CRIS	**CRIS**	**CRIS**

*patient and family or friend

Description of Measures

Screening Measures

Color-Word Interference Test or the Flanker Task will be used to determine an objective deficit in inhibition by a score of ≥ 1.5 standard deviations (SD) below the normative mean. The Delis-Kaplan Executive Function System (D-KEFS) was designed to detect executive dysfunction believed to be mediated by the frontal lobes. Since it is generally believed that solders, diagnosed with mTBI and PTSD due to blast injury, have damage to the frontal lobes, the Color-Word Interference Test of the D-Kefs will be used to screen for subjects that have, deficits in inhibition. The D-KEFS Tower Test, which is a version of the TOL, loads onto the same factor (Inhibition) as the Color-Word Interference Test (Latzman, 2010). Therefore, a deficit of ≥ 1.5 SD on the DKEFS Color-Word Interference Test would negate possible ceiling effects on the primary outcome measure. The test retest of the Color-Word Interference Test is suitable with a range of.49 to .86 for ages 20-49. The validity was "reasonable" for detecting patients with frontal lobe lesions from normal patients (Homack, 2005).

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. Patients that score at least 1.5 SD below the mean on the Flanker task will be included in the study. Secondary analysis will be conducted to determine the effect size on each of the EXAMINER tasks.

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.

Primary Outcome Measure: 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 45 minutes for each session (pre/post/follow-up). Each set consists of 70 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.

Stop Signal Task

An “X” or “O” stimuli is presented visually on a computer screen. Participants are asked to press the left button for an “X” and to press the right button for an “O” as quickly and as accurately as they can. If the stimuli are followed by an auditory tone (stop signal) they are asked to not press the button. Dependent measures are Response Time on Go Trials (RT) and Stop Signal Response Time (SSRT). Three sessions lasting approximately 10 minutes each will be conducted. Stop Signal will be used as a secondary outcome measure to determine the effect size.

Measures for Secondary Analysis

Beck Depression Inventory (BDI): 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).

Post-Traumatic Stress Disorder (PTSD) symptom checklist-military (PCL-M): The checklist is a 17-item self-report measure of the 17 DSM-IV symptoms of PTSD with a 5-point rating scale ranging from rarely to extremely frequent. The range of total score is 17 to 85. Internal consistency for the overall scale is .95 with cross validation to clinician-administered interviews ranging from .64 for Vietnam veterans to .83 for motor vehicle accident and assault victims (Weathers, 1991 & 1993; Blanchard et al, 1996). The PCL-M will be used to determine the impact of PTSD on the response to treatment.

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.

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). The index scores of the RBANS will be used to characterize the patient's cognitive capacity and to determine whether particular aspects of cognitive ability impact response to treatment.

Exploratory Generalization Measure

Generalization measures will be examined in a tertiary analysis to explore whether treatment effects generalize to everyday activities or participation in the community. Based on our previous study, treatment effect did not generalize to everyday activities as measured by the BRIEF-A. However, with the proposed methodological changes and the addition of functional practice with a Smartphone application, generalization to activities and community participation is anticipated to improve. The Metacognitive Index of the BRIEF-A was confirmed as a factor in our previous factor analysis and represents the executive function components targeted by GMT. The BRIEF-A was selected over the recommended common data element measure, the Frontal Systems Behavior Scale (FrSBe); since the FrSBe has not been tested in a homogenous TBI sample. While, our previous study did not reflect a significant improvement at the activity level, we will conduct a tertiary analysis to detect generalization using the BRIEF-A. In addition to the activity level of executive function, we would like to determine the effect of treatment at the community participation level. The TBI Outcomes Workgroup on common data elements (Wilde, 2010) has recommended the PART-O to measure participation in the community.

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 Metacogntive Index of the score of the BRIEF-A will be used to detect a change of executive functioning in the subject's home environment.

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.

7**. Statistical Methods**

Statistical Analysis Plan

Participants, who attend less than 90% of the treatment sessions, have medication changes during treatment that affect cognition and/or receive more than 5 hours of therapy (other than GMT) from a mental health specialist during the study will not be included in the final analysis.

Aim 1.

Aim 1 is to test the benefits of GMT for improving executive function.

Hypothesis 1a: GMT and home practice device will significantly improve problem solving ability compared to the control group (primary measure: time to completion on the Tower of London (cTOL). Since PTSD is prevalent and a potentially influencing co-morbidity, we will to investigate whether there is a significant interaction between treatment group and PTSD severity. Secondary measures include number of optimal moves on the TOL; and measures derived from the Stop Signal Task (SST; a measure of inhibition control).

Exploratory Hypothesis 1.b.GMT and functional practice will significantly improve everyday activities that require executive function skills (primary measure: Behavior Rating Inventory of Executive Function-Adult version, secondary measure: CRIS).

Analysis Plan for Hypothesis 1.a. and Hypothesis 1.b. To test the first specific aim (hypothesis 1a), the primary analysis will use two sample t-test to compare group A (intervention) and group B (control) on improvements in time to completion on the TOL. In addition, as an exploratory analysis, we will perform a regression analysis that includes treatment group, PTSD severity and their interaction as independent variables, to adjust for PTSD severity and to investigate whether there is interaction between treatment group and PTSD severity. Similar analyses will be performed for hypothesis 1 for secondary outcome variables of changes in index of optimal moves on the TOL and reaction time (RT) and accuracy on SST. To test hypothesis 1b, exploratory *tertiary analysis* using paired t-tests will determine whether treatment effect generalizes to executive function performance in everyday activities (BRIEF-A) or engagement in community participation (CRIS).

Aim 2

Aim 2 is to investigate factors which affect response to treatment.

Hypothesis 2a. Baseline cognitive ability, depression, sleep, and presence of PTSD will have a significant effect on response to treatment.

Analysis Plan for Hypotheses 2a. To test the second specific aim, a general linear regression will be used to determine whether any of the four factors is associated with response to treatment. The analysis will be restricted to the participants assigned to the intervention group. The dependent variable for the regression model will be 'time to completion' on the TOL, and the independent variables will be CWI, BDI-II, and PCL-M scores.

8. Possible Discomforts and Risks:

The potential risks are minimal for the proposed intervention (group therapy). The standard of care for Veterans with mTBI is to receive cognitive therapy in group or individual settings. The risks of the proposed research would not increase from the current risks that patients experience in traditional therapy.

Patients may become anxious when discussing the trauma, they experienced and the deficits they continue to face on a daily basis. Fatigue and/or anxiety may occur while performing screening tests and tests prior to each session. Subjects with attention and concentration deficits may have difficulty completing the testing within one session. The PI will monitor patient anxiety and recommend alternative therapies such as individual speech therapy and additional psychological services that are available to the patient.

9. Possible Benefits:

The proposed therapy has the potential to improve the subject's ability to organize and complete tasks by utilizing a strategy that can be used in various settings. The group therapy process also will provide peer support to help cope with the frustration of living with executive dysfunction. A group therapy also allows for more than one subject to receive therapy during the same time frame.

9. Conflict of Interest:

None of the investigators have a conflict of interest in any part of this study.