Rehabilitation of Executive Functioning in Veterans with PTSD and Mild TBI

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Abstract

Both posttraumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI) are prevalent in veterans from the Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) conflicts and have been associated with cognitive dysfunction, which may lead to functional impairment and poor community reintegration. PTSD can be highly debilitating not only due to emotional dysregulation, but also due to deficits in the cognitive control processes in areas of complex attention, executive functions, and learning. Deficits in these cognitive control functions important have been linked with difficulties in community reintegration, educational and occupational functioning in individuals suffering from both PTSD and TBI.

The overall aim of this proposal is to investigate the potential effectiveness (both short and longer term) of a training program that targets executive control functions of attentional self-regulation and goal management (GOALS), in Veterans with co-morbid posttraumatic stress disorder (PTSD), history of mild traumatic brain injury (mTBI), and cognitive difficulties. We will assess whether training in hypothetically targeted cognitive control mechanisms (attentional self-regulatory functions in particular) leads to improved functioning in other domains, such as daily task performance and emotional regulation.

The effects of the training will be evaluated on multiple domains of functioning:

We will assess whether training improves performance in targeted neuro-cognitive domains of complex attention and executive function, which are commonly impaired in veterans with both mTBI and PTSD.

Executive control functions arguably most need to be engaged in the low structure of real-world settings, where direction by external structure is not sufficient to guide behavior. We will assess whether training core executive self-regulatory control functions via personally-relevant activities, generalizes to improved functioning in settings that reflect the complex, low-structure nature of the real world, as reflected both in participants' performance on complex real-life tasks, and on self report of daily functioning.

We will assess whether training in core executive self-regulatory control functions generalizes to improvements in emotional regulation and control in participants everyday lives as reflected by self-report measures.

The primary aim of any training is to effect long term behavioral change post intervention. Long-term follow-up will be conducted to determine which aspects of the

intervention have enduring benefits, and in which domains. We predict that the GOALS approach of training core executive self-regulatory control functions, using functionally and personally-relevant activities and goals in participants' real lives, will make it more likely for training benefits to be incorporated maintained six months after training ends. This will be reflected by maintained improvement in multiple functional domains (neurocognitive, daily functioning and emotional regulation) relative to their baseline functioning.

Rehabilitation of Executive Functioning in Veterans with PTSD and Mild TBI

Provide a list of all abbreviations used in the protocol and their associated meanings.

PTSD: Post-traumatic stress disorder

mTBI: Mild traumatic brain injury

GOALS: Goal Oriented Attentional Self-regulation training – experimental

intervention

EDU: Brain Health Education – comparison intervention

OEF: Operation Enduring Freedom

OIF: Operation Iraqi Freedom

OND: Operation New Dawn

SFVAMC: San Francisco VA Medical Center

VANCHCS: VA Northern California Health Care System

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1.0 Study Personnel

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2.0 Introduction

Provide scientific background and rationale for study:

The overall aim of this proposal is to investigate the potential short and long term effectiveness of a cognitive training program that targets executive control functions in veterans with comorbid posttraumatic stress disorder (PTSD), history of mild traumatic brain injury (mTBI), and cognitive difficulties. Both PTSD and TBI have been associated with cognitive dysfunction which may lead to functional impairment and poor community reintegration. PTSD can be highly debilitating not only due to emotional dysregulation, but also due to deficits in the cognitive control processes. The most common cognitive deficits associated with both PTSD and TBI involve attention, executive functions, and memory. Attention and executive functions deficits commonly found in PTSD include working memory difficulties, problems in sustaining attention over time, response inhibition, and impaired ability to gate, monitor, and regulate the flow of incoming information and environmental stimuli. Deficits in these cognitive control functions important for goal-directed behavior have been linked with difficulties in community reintegration, educational, and occupational functioning.

Both PTSD and a history of mild TBI are prevalent in veterans from the Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) conflicts, with reported rates for each disorder ranging from 14 - 22%. A 2005 survey of Iraq/Afghanistan veterans found that for the 12% of 2235 respondents with a history of mild TBI, the strongest factor associated with persistent post-concussive symptoms was PTSD, even after removing overlapping symptoms. A recent study indicated that 44% of Iraq soldiers who reported history of mild TBI also met criteria for PTSD, and that PTSD may mediate the relationship between mild TBI and cognitive dysfunction. The incidence of PTSD rates tends to increase in relationship to the occurrence of TBI. A recent study examining TBI and PTSD service utilization of OIF veterans found that one-year postdeployment, 65% of those with mild TBI-PTSD reported seeking treatment for concerns related to reintegration. These findings strongly suggest that the combined syndrome of TBI-PTSD is common, complex, debilitating, and requires special consideration beyond each alone. The issues from TBI-PTSD include disruption of core cognitive and emotional regulation mechanisms that are essential for goal-directed functioning in daily life. Interventions that target cognitive and emotional self-regulatory functions may be particularly valuable in treating the combined PTSD-TBI syndrome.

Either TBI or PTSD independently may alter cognitive, emotional, and behavioral functioning. Disruption of control over information processing reduces the effectiveness of higher level functions such as learning, problem-solving and goal management. Additionally, difficulties with emotion regulation and control can significantly affect cognition and goal attainment. Emotional and cognitive control are directly tied together in that the underlying neural systems interact significantly in achieving self-regulatory control necessary for goal-directed behavior. Deficits in these cognitive control functions, important for goal-directed behavior, have been linked with difficulties in community reintegration, educational and occupational functioning. For example, individual experiencing feelings of anxiety and/or distress will likely be less able to effectively complete tasks that require overcoming challenges and solving problems. Similarly, it is

likely that reduced cognitive control would contribute to poorer emotional control. Individuals with TBI, with reduced self-regulatory control, may have more difficulty managing and altering negative and/or traumatic associations and the 'triggered' emotions. For example, an inability to filter out information and demands that are not directly related to a current goal may lead to increased feelings of being overwhelmed. Given the limitations of neural processing resources, it is expected that an increase in 'load,' whether from cognitive or emotional sources, would lead to less efficient overall functioning.

PTSD and mild TBI may have independent and additive roles, and may also interact at multiple levels, including at the genesis of injury, the maintenance of symptoms, different aspects of cognitive-emotional functioning, and at the level of neural mechanisms. Features of each may interact to worsen functioning and/or make treatment more difficult. Cognitive dysfunction may impede treatment for emotional problems, and emotional dysregulation may impede treatment of cognitive dysfunction. Severe emotional control dysfunction, including anxiety, hypervigilance, and avoidance, may become significant barriers to treatment of cognitive issues. On the other hand, cognitive deficits, especially those affecting aspects of attention, learning and memory, may become barriers to effective treatment of emotional issues. In current practice, most interventions are directed towards a diagnosis of PTSD or TBI, but not both. Treating PTSD, in the context of TBI, may differ from treating PTSD alone. For individuals in the chronic phase of the disorder, the PTSD treatments with the strongest evidence are cognitive-behavioral psychotherapies, such as cognitive processing therapy, as well as prolonged exposure therapy.

Modification of these approaches for individuals with cognitive dysfunction remains an important frontier for treatment. Current experience suggests that PTSD in individuals who also sustained TBI may be more complicated, and the chronicity of symptoms may be extended. Patients with TBI-PTSD may respond differently to standard treatments compared to those with only TBI or PTSD. Cognitive limitations may make it necessary to modify cognitive-behavioral therapies, and emotion regulation and impulse control problems may complicate the use of exposure techniques. Conversely, the emotional dysregulation, avoidance and potential for triggering may impede engagement in cognitive rehabilitation therapies.

These considerations argue strongly that treatments improving cognitive and emotional self-regulatory functions may be particularly valuable in treating the combined PTSD-TBI syndrome. The issues from TBI-PTSD include disruption of core cognitive and emotional self-regulation mechanisms that are essential for goal-directed functioning in life. Interventions that strengthen the goal-directed control functions, such as the selection of goal-relevant information along with inhibition of distracting information, may be particularly helpful towards improving the functionally important / integrated aspects of self-regulation that contribute to goal attainment. Dorsolateral prefrontal cortex and ventromedical prefrontal cortex interact in the regulation of emotions with modulation of amygdala. These interacting circuits are likely to be important for cognitive and emotional self-regulation training such as mindfulness-based attention regulation (MBSR). A recent study illustrated that a modified MBSR training program, Mindfulness-Based Mind Fitness Training, may help healthy military reservists preparing for deployment to regulate their emotions.

 Include summary of gaps in current knowledge, relevant data, and how the study will add to existing knowledge. The above background forms an important foundation for further development of interventions for combined TBI-PTSD syndrome. The ultimate goal will be to strengthen key underlying self-regulatory control functions that improve a person's ability to adapt, be resilient, problem-solve, and in general, accomplish his/her own personal goals. Although studies evaluating the effectiveness of cognitive training targeting executive control deficits in individuals with comorbid PTSD and history of mild TBI are clearly needed, to our knowledge there have been no published studies in this area.

We have developed a therapist-administered cognitive training program, Goal-Oriented Attentional Self-Regulation (GOALS) that targets executive control functions of applied mindfulness-based attention regulation and goal management strategies, and links them to participant-defined real-life goals. In contrast to training via practice on isolated tasks, this training protocol involves application of attention regulation skills and strategies to participant-defined goals in real life, ecologically valid settings. One of the main training aims is to improve self-regulatory control mechanisms as they contribute to goal attainment.

Two conceptual lines converged to delineate target processes for this intervention. First, pathways from perception to action require mechanisms for the selection of information for indepth processing, as well as the maintenance and protection of this information from both internal and external disruptions during working memory and subsequent learning, decisionmaking, and/or problem-solving. Second, many patients with executive control difficulties show an overall "life disorganization" or "goal neglect", with poor ability to manage and attain goals, even when they may be able to describe their intentions at the outset. We reasoned that selective maintenance of goal-related information, and protection from both internal (e.g. feeling anxious) and external disruptions are important for guiding sequences of steps (sub-goals) required to accomplish the goal. Therefore, intervening on these processes may help to ameliorate symptoms of goal neglect. The experimental training protocol was based on training interventions that have been applied to patients with brain injury as well as other populations. with special emphasis on mindfulness-based attention regulation strategies applied to progressively more challenging daily life situations and complex project-based functional tasks. Cognitive and emotional issues are addressed as they become important in achieving goals that are relevant to each individual participant. An overarching hypothesis is that training that improves self-regulatory goal-directed control over neural processing would benefit all subsequent stages of goal-based processing, by making more efficient, better integrated functional networks for the performance of relevant tasks, and ultimately goal attainment in real life contexts.

In a prior study, we assessed the feasibility and effectiveness of GOALS training in individuals with chronic brain injury. Following training, participants showed improvements in accomplishing complex functional tasks in unstructured environment, confirming generalization of training effects to ecologically valid settings. In testing whether functional improvements might be related to improvements in the targeted cognitive functions, we also assessed domain-specific changes utilizing neuropsychological testing. Participants who completed GOALS training also improved on neuropsychological measures of complex attention and executive functions, including working memory, mental flexibility, inhibition and sustained attention. Furthermore, fMRI results after training indicated significantly enhanced modulation of neural processing in extrastriate cortex and changes in prefrontal cortex.

We have been conducting randomized-control study of the effects of GOALS training with Veterans with a history of chronic TBI. Preliminary results indicate improvements on neuropsychological measures of attention and executive function, and performance on complex

real-life tasks. Furthermore, participants had post training improvements on self-report measures reflecting emotional regulation and emotional health. These findings further suggest that improving cognitive control (attentional self-regulation in particular) may also improve functioning in other domains including emotional regulation and complex daily tasks, leading to a novel hypothesis regarding the value of functional improvements in cognition for emotional health.

One of the main goals of any training is to encourage maintenance of benefits even after direct intervention ends. This is of particular practical importance given that therapist time with a patient is always limited. We designed the GOALS intervention to include extensive practice and active application of trained strategies in participants' daily life to maximize the likelihood that the benefits of training would continue beyond the interactions with the trainer. In a follow-up structured interview conducted six months to two years following completion of GOALS training, as many as 92% of participants with chronic brain injury reported that they have integrated and continued to use some of the trained strategies in their daily lives, even in the absence of reinforcements provided by training.

The overall aim of this proposal is to investigate the potential effects (both short and longer term) of Goal-Oriented Attentional Self-Regulation training program that targets executive control functions of attentional self- regulation and goal management in Veterans with co-morbid posttraumatic stress disorder (PTSD), history of mild traumatic brain injury (mTBI), and cognitive difficulties. We will assesses whether training in hypothetically targeted cognitive control mechanisms (attentional self-regulatory functions in particular) may lead to improved functioning in other domains, such as complex daily task performance and emotional regulation.

The results of these studies will inform us to what extent a functional approach, training core executive self-regulatory attentional control functions via personally-relevant activities, will be effective in improving functioning for Veterans with PTSD and mTBI. The study design will provide a test not only of potential benefits on real-life functioning, but also determine to what extent these benefits are related to actual changes in hypothetically targeted cognitive and emotional functions. These studies will provide a foundation for future studies to investigate the neural mechanisms that support improvements in these functions.

 Include rationale for including or excluding certain populations – in particular vulnerable populations.

Seniors are more likely to have confounding health or cognitive problems that could influence assessment data. The target group for the research study is returning OIF/OEF Veterans, majority of whom are under 65.

3.0 Objectives

- Describe the study's purpose, specific aims, or objectives.
- State the hypotheses to be tested.

The overall aim of this proposal is to investigate potential short- and long-term effects of a cognitive training program that targets executive control functions of attentional self- regulation

and goal management, Goal-Oriented Attentional Self-regulation (GOALS), in Veterans with comorbid PTSD - mTBI and cognitive difficulties.

Aim 1: Determination of short and long term effects of cognitive training on neuro-cognitive performance:

<u>Hypothesis 1</u>: Participants who perform GOALS training will demonstrate greater improvements on untrained standardized neuropsychological measures of complex attention and executive function compared to participants who participate in control EDU training.

<u>Hypothesis 2</u>: Improvements in complex attention and executive function will be sustained at six months post GOALS training, suggesting persistence of training benefits.

Aim 2: Determination of short and long term effects of cognitive training on complex real-life functional task performance and daily functioning:

<u>Hypothesis 1</u>: Participants who perform GOALS training will demonstrate greater improvements on untrained complex real-life functional task performance compared to participants who participate in control EDU training.

<u>Hypothesis 2</u>: Participants who perform GOALS training will report greater improvements on self-report measures of daily functioning compared to participants who participate in control EDU training.

<u>Hypothesis 3</u>: Improvements in complex functional task performance and on self-report measures of daily functioning will be sustained at six months post GOALS training, suggesting persistence of training benefits.

Aim 3: Determination of short and long term effects of cognitive training on emotional regulation:

<u>Hypothesis 1</u>: Participants who perform GOALS training will report greater improvements on self-report measures of emotional regulation compared to participants who participate in control EDU training.

<u>Hypothesis 2</u>: Improvements on self-report measures of emotional regulation measures will be sustained at six months post GOALS training, suggesting persistence of training benefits.

4.0 Resources and Personnel

Include where and by whom the research will be conducted.

Research activities will take place at San Francisco VA Medical Center (SFVAMC) and VA Northern California Health Care System (VANCHCS) in Martinez. Drs. Neylan and Abrams will engage in study activities at SFVAMC. All other research personnel will engage in study activities at both locations.

Provide a brief description of each individual's role in the study. Be sure to
indicate who will have access to protected health information and who will be
involved in recruiting subjects; obtaining informed consent; administering
survey/interview procedures; and performing data analysis.

Principal Investigator:

Tatjana Novakovic-Agopian, PhD: Oversee the scientific, clinical and administrative aspects of the study and manage research activities.

Co-Investigators:

Anthony J-W Chen, MD: Consult on neurological assessment and treatment of mTBI and management of multi site studies.

Gary Abrams, MD: Consult on neurological assessment and treatment of mTBI and assist with recruitment.

Thomas Neylan, MD: Consult on all PTSD-related activities in the study including recruitment and clinical evaluation.

John Mc Quaid PhD: Consult on cognitive behavioral training and assist with recruitment

Study Coordinator:

Deborah Binder, MS: Manage data, assist in recruitment, screening and multi-site logistics, coordinate submission of IRB documents and responsible for human subjects regulatory compliance

Research Associates:

Fred Loya, PhD: Screen potential subjects, obtain consent, and either administer assessments (as blinded evaluator) or implement interventions for subject that he is not evaluator.

Michelle Murphy, PsyD: Screen potential subjects, obtain consent, and either administer assessments (as blinded evaluator) or implement interventions for subject that she is not evaluator.

Maya Bruhns, MA: Screen potential subjects and implement interventions.

Annemarie Rossi, MS OTR/L: Screen potential subjects and implement interventions.

Gerald Carlin, MS: OTR/L Implement interventions.

Nicholas Rodriguez, BA: Assist with administrative aspects, recruitment, screening, data management.

All of the research team will have access to protected health information and will be involved in recruiting subjects.

 If applicable provide information on any services that will be performed by contractors including what is being contracted out and with whom. N/A If applicable provide information on any Memoranda of Understandings (MOUs) or Data Use Agreements (DUAs) that are being entered into including with whom and for what reason. N/A

5.0 Study Procedures

5.1 Study Design

 Describe experimental design of the study. Include sequential and/or parallel phases of the study, including durations, and explain which interventions are standard of care.

The proposed study includes two interventions, as well as pre- and post-intervention assessments.

Participants who meet the inclusion criteria will be enrolled in the study and randomized to either a five-week comparison intervention (Brain Health Education - EDU) or an experimental intervention (Goal-Oriented Attentional Self-regulation training – GOALS).

After 5 weeks, those who enter with EDU will receive 5 weeks of GOALS, while those who begin with GOALS will have no further formal training.

Both groups will participate in assessments at baseline, week 5 and week 10. Long-term followup will be conducted at 6 months.

Time Commitment: Assessment: Neurocognitive assessments and self-report forms take up to 3 hours and functional assessments take up to 2 hours to complete, or up to 4 hours combined. Assessments may be completed in one or two sessions. Participants are free to take breaks during testing sessions. Participants participate in assessments four times during the course of the study (baseline, at 5 weeks, at 10 weeks, and at 6 months), or up to 20 hours (5 hours x 4 time points).

Participants will be randomly assigned to one or two 10-session interventions (GOALS and EDU), each lasting about 5 weeks. Intervention sessions last about 2 hours, with 2 group sessions per week and 3 one-hour individual sessions over the period of training. Participation in GOALS alone requires about 63 hours total (20 hours group sessions, 3 hours individual sessions, 20 hours homework, and up to 20 hours assessments). Participation in both GOALS and EDU requires about 106 hours total (40 hours group sessions, 6 hours individual sessions, 40 hours homework, and 20 hours assessments).

The interventions do not involve standard of care.

• Include a description of how anticipated risk will be minimized and include an analysis of risk vs. potential benefit.

Potential risks are minimal. The research procedures involved in this study present no physical risk and minimal psychological risk to the subjects. The primary risk in this study is the potential for anxiety (including possibility of exacerbation of PTSD

symptoms), discomfort or boredom associated with completing assessments and interventions. The test battery is relatively brief and is non-invasive. It consists of instruments (neuro-cognitive and functional assessments and self-report questionnaires) that have been previously administered to different patient populations, thus the potential for creating undue anxiety or frustration is minimal. There is a possibility of fatigue or boredom during presentation of information during interventions and performance of cognitive tasks.

All information will be kept confidential in accordance with all regulations as specified by the Department of Veterans Affairs. Any injuries that are a direct result of research procedures will be treated at no cost to the participant. Any adverse events will be reported immediately to the Institutional Review Board of the VA/UCSF. All associated personnel will have human subjects training and certification. All patients will be given a copy of their informed consent and encouraged to ask questions if they have any concerns.

Another potential risk is related to training taking place in a small group setting. Other research subjects within the group may become aware of personal information about other subjects. Researchers will ask all subjects to keep private all information learned about other group members and to not talk about this information outside the group sessions. If a subject expresses concern about another subject divulging personal information outside the research setting, research staff will inform the study investigator. The study investigator will then contact the subjects in question to address any breaches of privacy or confidentiality. However, we cannot guarantee that other subjects will not talk about other subject's personal information outside the group.

<u>Cognitive Testing</u>: There is a possibility of frustration from poor performance or fatigue. Cognitive testing will stop if a patient displays frustration or appears tired.

<u>Cognitive training</u>: There is a possibility of fatigue or boredom from performance of cognitive tasks. Participants are allowed frequent breaks during training. Participants are allowed frequent breaks during training. For patients, training will be adjusted for the fatigue level, and training sessions will stop if patients are frustrated or fatigued. Thus far, participants have generally expressed positive experiences with training.

It is possible that participation in the study may lead to an exacerbation of PTSD symptoms. All research staff directly working with participants have previous training and experience in working with this Veteran population (e.g., neuropsychologists; neuropsychology trainees; occupational therapist, certified rehabilitation counselor, etc.). Additionally, prior to contact with subjects, all research staff will undergo investigator-led training to confirm they recognize symptoms associated with PTSD/mTBI, such as subject reports of, or behavior that reflects: reexperiencing the traumatic event, avoidance, increased anxiety, emotional arousal, anger and irritability. Research staff will be instructed to communicate such manifestations as soon as possible to the study investigators, who are licensed clinicians with expertise in the assessment and management of symptoms associated with PTSD and brain injury. A study investigator will immediately attempt to contact the subject for a telephone assessment, or if indicated, to schedule an in-person assessment. Further action will be based on an assessment of the subject. Possible actions may include referral for additional appropriate clinical evaluation and/or follow-up treatment and possibly terminating the subject's participation in the study. If a

subject is withdrawn from the study due to increased symptoms, the study investigator will personally inform the subject of the decision to terminate involvement and may refer the subject to follow-up treatment if the subject is significantly distressed over being withdrawn.

In the event a subject manifests increased PTSD symptoms that are not minor and transient, the investigator will complete Form 119: Report of Unanticipated Serious Adverse Event (SAE) and/or Unanticipated Problem (UAP) Involving Risks to Participants or Others.

If a subject expresses concern about another subject divulging personal information outside the research setting, research staff will inform the study investigator. The study investigator will then contact the subjects in question to address any breaches of privacy or confidentiality.

Research staff will notify the study investigator within 24 hours if any subjects report or manifest more than minor and transient distress. The study investigator will contact the subject to evaluate the situation and determine if clinical referral is warranted. If a referral is warranted, the study investigator will inform the subject that a referral for treatment will be made. When making the referral, the study investigator will request that the subject's privacy be respected when scheduling the appointment.

All research staff will be trained in the above procedures. The research team will also meet or have conference calls weekly to discuss study activities and any issues or concerns about subjects. The research staff at both study sites is the same.

The potential risks in this study are balanced by the potential benefit for participants or their families. Some of the procedures involve cognitive task practice and training that may improve certain specific cognitive skills. Prior research with individuals with chronic TBI has suggested that participation in this cognitive training may be beneficial towards improving executive control skills. The focus of the current study is to test whether individuals with PTSD and mild TBI would also benefit from this training. The findings from these studies may potentially contribute towards improving rehabilitation for patients with Posttraumatic Stress Disorder and mild TBI, leading to an indirect benefit to society.

The findings from these studies may potentially make a major impact in improving rehabilitation for patients with Posttraumatic Stress Disorder and mild TBI, leading to an indirect benefit to society. Improved treatments for executive control and emotional dysfunction would potentially make a major impact in improving outcomes after exposure to traumatic events. The findings from these studies will be presented to health care workers and to other scientists in the field, and this is expected to influence both clinical care and future scientific investigations.

This research is designed to contribute to improving care by (1) providing a neuroscientific framework for understanding neurorehabilitation therapies and their effects on executive control functions and emotional regulation; and (2) aiding in the design of novel therapeutic interventions that more directly target the underlying cognitive bases of dysfunction. Completion of the proposed studies will provide an essential foundation for the immediate next steps -- directly targeting the elucidated neural pathways using improved behavioral, physiological (e.g. transcranial magnetic stimulation) and pharmacologic modulation treatment interventions.

 Provide description of the study population (delineate all categories of subjects – patients, providers, family members, employees, etc.). Include anticipated enrollment numbers

Total planned enrollment is 54. Subjects will be Veterans, ages 18 to 55 years, with at least 12 years of education, a current diagnosis of PTSD (DSM IV-R), and a history of mild traumatic brain injury.

- As applicable, provide information on any added protections for vulnerable populations. N/A
- If applicable include information on data and specimen banking. N/A

5.2 Recruitment Methods

• State how many subjects will be needed.

About 80 subjects will be recruited and enrolled to meet the enrollment target of 54, out of which it is anticipated 42 will complete the study.

• Describe when, where, how and by whom potential subjects will be identified and recruited.

Recruitment material includes a brochure, flier, and letters to potential participants, clinicians, and service providers. Participants will not be cold called. Researchers will call potential participants only if returning a call or a request to call (e.g., if potential participant left a note requesting phone contact). Recruitment activities will include presentations to individuals and groups associated with PTSD, as well as distribution of approved letters, brochures and flyers. Recruitment activities will target VA clinicians, VA Outpatient Clinics, Veteran Centers, State of California Department of Rehabilitation Veteran Services Programs, Employment Development Department Veterans Outreach programs, County Veterans Services, college programs for veterans, and Travis AFB Transition Service Center, as well as mental health and neurology clinics in local hospitals. Brochures and fliers will be placed in locations approved by the facility being visited, e.g., bulletin boards and brochure display tables. Clinicians on the research team may also provide an-IRB approved brochure or letter to selected patients who may be interested

<u>Step-by-Step Recruitment Process</u>: Research team members will contact or visit the above entities and request permission to leave off brochures, flyers and letters and will also ask if any clinicians or other service staff might be interested in hearing more about the research. If so, researchers will schedule a presentation to clinicians or service providers. Clinicians or service providers may invite potential subjects to these presentations. Brochures, flyers and letters will be available for distribution at presentations. If clinicians or service providers contact the researchers to refer a potential subject, they will be asked to have the subject initiate contact with the research team. If a potential subject expresses interest in person (e.g., at a presentation or if simply observing brochures being distributed), a telephone appointment will be scheduled to discuss the possibility of participation.

Researchers will follow the 'Initial Contact Script' for the first telephone contact with potential subjects. The Informed Consent will be reviewed during this initial telephone contact. If the potential subject continues to express interest and is not clearly ineligible, a telephone screening interview will be scheduled.

If the potential subject continues to express interest by the end of the telephone screening interview, a research clinician or rehabilitation specialist (e.g., neuropsychology fellow, certified rehabilitation counselor) will review the medical record in CPRS. Documents reviewed in the medical record will be those pertinent to eligibility criteria, e.g., diagnosis of PTSD, history of mTBI (not moderate or severe), neurocognitive and psychological testing reports, medication history, current symptoms, evidence of substance abuse, etc. A summary of the medical record review will be provided to the study investigator, who will determine whether the potential subject appears likely eligible and therefore a candidate for the second, in-person screening.

The types of medical records we may review to assess eligibility include: Patient History and Physical Examination, Discharge Summary(ies), X-rays and other Imaging Reports, Diagnostic/Laboratory tests, Drug Abuse Information, Alcoholism or Alcohol Use, Operative Report(s), Progress Notes, and Mental Health (not psychotherapy notes).

If potential subject appears likely to be eligible, the investigator will contact him/her and schedule an appointment for a consent and more in-depth eligibility interview and screen. At this in person meeting, the investigator will go through the informed consent process with the potential subject, including reviewing and signing Form 10-3203 if the subject is agreeable to being videotaped

The above process can be summarized as follows: Screen 1 \rightarrow Medical Record Review \rightarrow Summary to Investigator \rightarrow Investigator determines if Screening 2 to be scheduled \rightarrow Screening 2 (in-person).

A second pathway for Medical Record Review occurs when investigators identify potential subjects through CPRS medical record review or by VA providers providing names of Veterans who may quality (with HIPAA waiver), in which case medical record review takes place <u>before</u> telephone screening. In this case, investigators will assess eligibility of potential subjects through review of medical records in the CPRS database. The subgroup of patients identified as potentially eligible will be sent letters introducing the study to them. The letter will include contact information if they are interested in further information about the study. If the researchers do not hear back from potential subjects within 2 weeks of sending the letter, they will contact the potential subjects once to confirm receipt of letter and ascertain interest.

This second process can be summarized as follows: Identify Potential Subject → Medical Record Review → Send Letter → Follow-up Call (if no hear) → Screen 1 (if interested) → Summary to Investigator → Investigator determines if Screening 2 to be scheduled → Screening 2 (in-person).

 Describe materials that will be used to recruit subjects, e.g., advertisements. Include materials as an appendix or separate attachment.

Recruitment material includes a brochure, flier, and letters to potential participants, clinicians, and service providers.

 Describe any payments to subjects, including the amount, timing (at the end of the study or pro-rated for partial study participation), method (e.g., cash, check, gift card), and whether subjects will experience a delay in receiving the payment. Participants will be paid \$20/hour for the in-person Consent meeting and final screening, \$100 per testing session and \$.55 mile for over 20 miles each way for travel to testing or interventions. If Participants do not participate in any further study activities after the consent/screening meeting, they will be paid by mailed check within 6-8 weeks. If they continue to participate, they will be paid by mailed check within 6-8 weeks of participation in testing sessions. If they decide to withdraw from the study, they will be paid by mailed check in 6-8 weeks after any testing time they already completed before withdrawing.

5.3 Informed Consent Procedures

 Indicate if informed consent will be obtained and/or or if you are requesting a waiver of informed consent or waiver of documentation of informed consent. If the research involves multiple phases, specify for which phases of the research the waiver(s) is being requested and/or the informed consent will be sought.

Informed Consent will be obtained.

 Describe who will be obtaining informed consent, if applicable, and any circumstances that may need to be addressed (e.g. subjects with impaired decision making ability and the use of a legally authorized representative, etc.)

The principal investigator will train all research staff in documenting and obtaining informed consents. No subjects will have impaired decision making ability or require the use of a legally authorized representative.

 If applicable, indicate how local site study personnel will be trained regarding human subjects protections requirements and how to obtain and document informed consent.

The same research staff will be at both sites. All research staff will be trained in obtaining and documenting informed consent.

5.4 Inclusion/Exclusion Criteria

 Describe the criteria that determine who will be included in or excluded from the study.

Inclusion Criteria: Veterans, ages 18 to 75 years, with at least 12 years of education, a current diagnosis of PTSD (DSM IV-R), and a history of mild traumatic brain injury, defined by the American Congress of Rehabilitation Medicine (ACRM) and VA, as a traumatically-induced physiological disruption of brain function as demonstrated by at least one of the following: (1) loss of consciousness of up to 30 minutes; (2) any loss of memory for events immediately before or after the event; (3) any alteration in mental state at the time of the event, for example feeling dazed, disoriented, or confused; and (4) a focal neurological deficit or deficits that may or may not have been transient, for example loss of coordination, speech difficulties, or double vision.

Participants must be in the chronic, stable phase of recovery (>6 months from injury), with residual cognitive difficulties that are affecting daily functioning; on stable psychoactive medications (> 30 days); and able and willing to commit to participate in 10 weeks of training and assessments.

The original inclusion criteria included OIF/OEF/OND Veterans, ages 18 to 55 years, with 12-16 years of education. The protocol was amended to eliminate the OIF/OEF/OND requirement, raise the age limit to 65, and extend the education years. The rationale for these changes were to: 1) expand number of potential subjects to increase likelihood of reaching study enrollment target; 2) increase the eligibility pool to include older veterans with PTSD who may be able to benefit from cognitive interventions, given that PTSD symptoms can last for several years, even decades, after the original trauma; and 3) to expand the eligibility pool to include veterans with more than 4 years of college education, as many veterans have more than 4 years of college.

The amended inclusion criteria included Veterans, aged 18 to 65 years. The protocol was amended to raise the age limit to 75 years. The rationale for this change was to once again expand number of potential subjects to increase likelihood of reaching study enrollment target; 2) increase the eligibility pool to include older veterans with PTSD who may be able to benefit from cognitive interventions, given that PTSD symptoms can last for several years, even decades, after the original trauma.

Exclusion Criteria: A history of moderate or severe TBI (defined by ACRM as having an injury that includes a loss of consciousness lasting longer than 30 minutes, or post-traumatic amnesia lasting longer than 24 hours). Unstable medical, neurologic, or psychiatric condition, including severe cognitive dysfunction, or other reasons for being unable or unwilling to participate in the training and assessments; ongoing illicit drug or alcohol abuse (AUDIT>8); psychosis, severe depression, anxiety or PTSD precluding participation in research activities; current (past 60 days) evidence-based PTSD remediation therapy; poor English comprehension. Eligible participants may have other co-morbid stable neuropsychiatric disorders, including depression. There will be no restriction in regard to gender, race and socioeconomic status.

Inclusion and Exclusion criteria will be verified through the first screening telephone interview (e.g., English speaking ability), medical record review and assessment by the principal investigator during the in-person screening interview.

To ensure that participants' providers (e.g., PCPs and mental health providers) are aware of their participation in a research intervention, we will work with local facilities to flag in CPRS that the patient is enrolled in a cognitive rehabilitation research study. Both the participant and his/her providers will be informed that unless it is medically contra indicated, the participant should stay on the same therapy regiment (particularly with regard to psychoactive medications regiment, or new evidence based behavioral interventions) for the 6 month duration of the study.

5.5 Study Evaluations

 Describe all evaluations to be conducted (including screening; tests/questionnaires that will be administered; any procedures that subjects will be required to complete) and data collection methods. Include materials as an appendix or separate attachment.

Mayo Portland Adaptability Inventory (Malec, et al. 2001), Goal Processing questionnaire; Novakovic-Agopian, Chen, Rome 2007), Profile of Mood States (Lorr and McNear et al., 1988), PCL-M (PTSD Checklist - Military Version), Auditory Consonant Trigrams, Digit Vigilance, Delis-Kaplan Executive Function System (DKEFS), Hopkins Verbal Learning Test - HVLT-R, Brief Visual Memory Test Revised - BVMR-R, Trails A, Trails B, Wechsler Test of Adult Reading-WTAR (Psychological Corporation, 2001), Letter Number Sequencing, WAIS IV, Goal Processing Scale (Novakovic-Agopian, Chen et al 2012), Clinician-Administered PTSD Scale (CAPS- Blake et al, 2000), Beck Depresion Inventory, Difficulties in Emotional Regulation Scale (Gratz and Roemer, 2004). There is also a screening questionnaire.

Mayo Portland Adaptability Inventory does address substance abuse. However, The purpose of the data is to conduct scientific research and that no personnel involved in the study may identify, directly or indirectly, any individual patient or subject in any report of such research or otherwise disclose patient or subject identities in any manner that would suggest the individual patient or subject has been involved or referred to any drug or alcohol treatment program.

The evaluator will videotape the Goal Processing Scale functional assessment if the subject agreed and signed the VA 10-3203 Consent form and continues to agree to being videotaped during the assessment. The subject has the option to refuse this without affecting participation in the study. The video camera will be placed unobtrusively by the subject. Videotaping GPS sessions will allow the evaluator to review the functional assessment later to address any questions or issues related to rating subject performance. Videotaped assessments may be reviewed by other raters to confirm ratings. Videotapes will be stored in locked cabinets in locked VA offices and viewed in locked VA offices.

5.6 Data Analysis

• Provide sample size determination and analysis (include anticipated rate of screen failures, study discontinuations, lost to follow-up etc.).

We estimated sample size requirements for the primary hypotheses for each aim based on the actual preliminary data from veterans who underwent GOALS training. For Attention and Executive Function Overall Domain z score (AVEXE) we found a standardized effect size of 1.2, for the GPS Overall Domain Score (GPSTA) and the Mayo Portland Adaptability Inventory Total Score (MPTST) we found a standardized effect size of 1.1, and for the POMS Total Mood Disturbance Score (POMSTMDZ) we found a standardized effect size of 0.8. Therefore, using the lowest effect size we would estimate that a feasible sample size of 42 patients (21 per group) for each intervention (GOALS and EDU) should yield a power of .80 at an alpha level of 0.05 to detect a standardized effect size of 0.8 or larger.

• Describe how, where and by whom the data will be analyzed.

Tests of repeated measures will be used to assess the effects of the training interventions on pre- and post- intervention measurements. Intervention group x time interactions will be assessed using ANOVA and specific relationships will be tested using paired T-tests.

Practice Effects: Because of repeated testing, improvements on some assessments may be partially due to practice. As a sensitivity analysis, we will compare tests using absolute change scores (as described above) to those using a change index that corrects for practice effects [70]. Specifically, change is operationalized as ((X2-X1)-(M2-M1))/SED, where X1, M1, and X2, M2 are the baseline and follow-up scores for a participant and corresponding group means, respectively; SED is the standard error of the difference. These results will be compared to those obtained from the regression models.

The PI and co-investigators will perform data analysis.

5.7 Withdrawal of Subjects

 Describe any anticipated circumstances under which subjects will be withdrawn from the research without their consent.

A subject may be withdrawn if the event of severe increase of PTSD symptoms, disruptive behavior (e.g., yelling during sessions, conflict with another subject), non-compliance (e.g., never attends training sessions), changes in medical condition (e.g., severe illness precluding participation), changes in psychotropic medications, and unforeseeable circumstances (e.g., death in family; offer of full-time employment).

 Describe the consequences of a subject's decision to withdraw from the research and the procedures for orderly termination of participation by the subject (e.g., the subject contacting the investigator for an end-of-study visit).

Participants are told they can withdraw at any time. Should the investigator decide to terminate a subject's participation, she will contact the participant to discuss the reasons for termination. The investigator will also make a follow-up appointment if requested by the participant to discuss further any concerns expressed by a participant.

6.0 Reporting

 Include procedures for reporting unanticipated problems, serious adverse events, and protocol deviations.

All research staff has been directed to document unanticipated problems or adverse events and to notify the Principal Investigator of any unanticipated problem or adverse event. Investigators will follow up with subjects (in person or by telephone call) until the resolution of the adverse event and will ensure that appropriate medical care is provided. Researchers will complete SAE

or UAP reports. Reports will be submitted to the VA Central IRB within 5 business days after the reporting individual becomes aware of the occurrence.

7.0 Privacy and Confidentiality

• Describe whether the study will use or disclose subjects' Protected Health Information (PHI).

Screening subjects will include review of VA medical records.

 Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, Certificates of Confidentiality, and separation of identifiers and data)

Electronic data will be stored on VA computer hard drives and server, all encrypted per VA guidelines. Paper records will be kept in locked cabinets in locked VA offices.

If VA desktop computers are unavailable (e.g., being used by other researchers), research staff may use VA laptops to enter/save research data (e.g., de-identified test scores) and then transfer data to r drive directly from laptop or, if applicable, transfer to VA desktop computer via USB drive. Researchers will also use laptops for email and files that don't involve subject data (e.g., research design, materials for presentations or publications, if desktop computers unavailable or if out of the office).

The USB drives have security features (activated by thumb swipe or password) that prevent them from being used by anyone other than the researcher to whom they are assigned. Researchers may use the USB drives to transfer information from a VA laptop to a VA desktop computer for further data entry/calculations when the desktop computer becomes available. The data would be uploaded to the VA server when data entry/calculation is complete.

8.0 Communication Plan

- Include plan for ensuring all required local site approvals are obtained and notifying the Director of any facility where the research in being conducted but the facility is not engaged.
 - N/A both sites are engaged
- Include plan for keeping all engaged sites informed of changes to the protocol, informed consent, and HIPAA authorization
 - The staff will be the same at both sites.
- Include plan for informing local sites of any Serious Adverse Events,
 Unanticipated Problems, or interim results that may impact conduct of the study.

- Notify by telephone and email local facility's institutional official and R & D
 Committee of any SAE, UAP and interim results that may impact conduct of the study
- Complete and submit SAE/UAP documentation as required by the local facility and local facility's R&D Committee. These documents will be uploaded to the Central IRB website
- Include plan for ensuring the study is conducted according to the IRB-approved protocol.
 - Prior to implementation of study, thoroughly train all research team members in study and IRB procedures and documents
 - Create and distribute written study procedure protocols kept in paper and electronic copy formats
 - Distribute IRB materials on procedures and report forms and maintain current IRB materials in paper and electronic copy formats
 - Hold weekly conference calls to address questions and resolve issues regarding study conduct, protection of human subjects, and IRB guidelines and forms.
 - Encourage open communication between research team members and PI/SC to address questions or concerns about study procedures and protection of human subjects. Open communication will be encouraged by holding weekly meetings and/or conference calls in which the PI specifically asks members of the team to voice questions and concerns about any aspect of the study. The PI will also encourage the research staff to email or call about issues or concerns if they prefer to use those channels.
- Include plan for notifying all local facility directors and LSIs when a multi-site study reaches the point that it no longer requires engagement of the local facility (e.g., all subsequent follow-up of subjects will be performed by the PI from another facility).
 - The PI/SC will notify the Local Facility Director in writing (paper and email) when the study no longer requires engagement of the local facility

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