Rehabilitation of Executive Functioning in Veterans with PTSD and Mild TBI

Study ID: D1111-I

ClinicalTrials.gov ID: NCT01921179

Protocol Abstract for 2019 Continuing Review of PTSD-mTBI Study
03/26/2019

- Instructions: Include a 1-5 page (do not exceed 5 pages) abstract containing the following content (as applicable). Please attach a separate PDF document.

Purpose
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 co-morbid 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

Research questions and Hypotheses
Question 1: What are short and long term effects of GOALS training on neuro-cognitive performance in Veterans with co-morbid PTSD and Mild TBI?

- *Hypothesis 1:* Participants in GOALS training will demonstrate greater improvements on untrained standardized neuropsychological measures of complex attention and executive function compared to participants in EDU training.
- *Hypothesis 2*: At the six month follow-up, participants will on average demonstrate improvements on standardized neuropsychological measures of complex attention and executive function relative to their baseline performance, suggesting persistence of GOALS training benefits.

Question 2: What are short and long term effects of GOALS training in veterans with co-morbid PTSD and Mild TBI on complex real-life functional task performance and daily functioning ?

- *Hypothesis 1*: Participants who participate in GOALS training will demonstrate greater improvements on an untrained complex real-life functional task than participants who participate in control EDU training.
- *Hypothesis 2*: Participants who participate in GOALS training will report greater improvements on self report measures of functional performance in their daily lives compared to participants who participate in control EDU training.
- *Hypothesis 3:* Training benefits will persist six months post GOALS training, as measured by participants' improvements in complex functional task performance and on self-report measures of everyday functional performance, relative to their pre-GOALS performance

Question 3: What are short and long term effects of GOALS training in veterans with co-morbid PTSD and Mild TBI on self-report measures of emotional regulation?

> *Hypothesis 1:* Participants who participate in GOALS cognitive training will report greater improvements on self report measures of emotional regulation compared to participants who participate in control EDU training.
> *Hypothesis 2*: At six month follow-up, participants will demonstrate improvements on self report measures of emotional regulation relative to their pre-GOALS performance, suggesting persistence of training benefits.

Methods

Eligibility criteria

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.
Exclusion Criteria: 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 evidence-based PTSD remediation therapy; and, poor English comprehension.

Interventions

Participants who meet the inclusion criteria will be enrolled in the study and randomized to either five week Brain Health Education (EDU) or Goal-Oriented Attentional Self-regulation (GOALS) training. 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 follow-up will be conducted at 6 months.

The GOALS training involves ten 2 hour sessions of group-based training, three individual 1 hour training sessions, and approximately 20 hours of home practice. It is conducted in a small group format with 2-5 participants, and 2 therapists per group.

The GOALS intervention emphasizes two key components: First, regulation of distractibility (redirection of attention to goal-relevant processes and the filtering of non-relevant 'noise', especially in the context of distractions) is addressed with attention regulation training. Training emphasizes principles of applied mindfulness-based attention regulation to redirect cognitive processes towards goal-relevant activities even when distracted. Second, these goal-oriented attentional self-regulation skills are practiced in daily life and actively applied to self-generated complex goals. Participants are asked to identify personally-relevant and feasible functional goals as individual and group projects. They are then trained in applying the goal management strategies on the functional task(s) of their choice. The main objective is to allow extensive practice and application of skills, thereby linking the attentional regulation directly to goal attainment efforts.

The EDU training is an active comparison matched with GOALS for therapist time, for homework load, and participation in a group. It involves ten 2 hour sessions of group-based training, three individual 1 hour training sessions, and approximately 20 hours of home practice. It is conducted in a small group format with 2-5 participants and 2 therapists per group. The EDU training is designed to be engaging and provide information about brain functioning and brain health.

Assessments

At baseline (pre GOALS or EDU), week 5, week 10 (post GOALS for those who began with EDU), and at 6 months, participants will be evaluated with a multi-level battery of measures assessing:

1. Neuro-cognitive performance focusing on neuropsychological measures of complex attention, executive function and memory.
2. Functional performance on complex 'real-life' tasks involving multitasking and goal management
3. Emotional regulation and daily functioning.

Neuropsychological Assessment: The neuropsychological battery used in this study was developed to assess performance in cognitive domains of *complex attention and executive function* that are commonly affected by both TBI and PTSD and targeted by GOALS training. *Working Memory* will be assessed with (1) Letter Number Sequencing, WAIS IV and (2) Auditory Consonant Trigrams. *Sustained attention* will be assessed with the timed Digit Vigilance test. *Inhibition of Automatic Responding* will be assessed with DKEFS Stroop Inhibition (time and error score). *Mental Flexibility* will be assessed with: (1) Trails B and (2) DKEFS Stroop Inhibition-Switching. Performance on *verbal memory* tests will be assessed with Hopkins Verbal Learning Test - HVLT-R.

Participants' performance in cognitive domains commonly affected by TBI and PTSD, but not targeted by the intervention, will also be assessed as a marker of potential non-specific changes. *Processing speed* will be assessed with (1) Trails A, requiring rapidly connecting in order numbers on a page, and with (2) DKEFS Stroop Color Naming and (3) DKEFS Stroop Word Reading. Intellectual functions estimate will be assessed at baseline with Wechsler Test of Adult Reading- WTAR. The purpose of the WTAR is to estimate pre-morbid intellectual ability. The overall battery of neurocognitive tests will take approximately 1 hour.

Functional Assessment: To address the functional and ecological limitations of conventional clinical neuropsychological tests in characterizing executive dysfunction, we included functional assessments in the neurobehavioral test battery. Participants will complete complex 'real-life' functional assessment task using the Goal Processing Scale (GPS). To control for practice effects of repeated administrations GPS has three alternate forms. The GPS domains assessed include*: Planning, Initiation, Maintenance of Attention, Self-Monitoring, Sequencing and Switching Attention, Flexible Problem Solving, Memory, and Executio*n.

The evaluator will videotape the GPS 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.

Self-Report Measures: Emotional regulation / mood disturbance measures will include Profile of Mood States, Clinician-Administered PTSD Scale (CAPS), PTSD Checklist-Military Version (PCL-M), and Difficulties in Emotional Regulation Scale. Daily Functioning measures will include: Mayo Portland Adaptability Inventory and Goal Processing Questionnaire (GPQ).

Follow-up
At 6 months post-baseline, participants will be re-evaluated with the above-described multi-level battery of measures.

Data Safety Monitoring Plan
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 by the PI to the Central VA. 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.

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

Cognitive training: There is a possibility of fatigue, frustration, or boredom from performance of cognitive tasks. 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: re-experiencing 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.

Progress to date

- Study was conducted at both SFVAMC and VA NCHCS in Martinez sites.
- Staff was hired and trained in study recruitment, assessment and cognitive training procedures.
- Study actively recruited subjects at both sites:
    - 545 letters describing the study have been mailed to potential participants; 218 detailed telephone screens have been conducted; 76 participants have been enrolled.
- To help enhance recruitment, researchers has made extensive efforts to enroll Veterans, including providing IRB-approved recruitment material to VA Outpatient clinics, Veteran Centers, State of California Department of Rehabilitation Veteran services programs, State of California Employment Development Department disabled Veterans outreach, State of California County Veterans services, community college Veteran affairs offices.
- Presentations describing the aims of this study have been made by PI and co-investigators to clinicians and researchers at both SFVAMC and VA NCHCS in Martinez, and at the: VINS21 TBI Polytrauma meeting 2014, 2015, 2016; and 2018; American College of Rehabilitation Medicine Conference October 2015; VA Psychology Leadership Conference May 2015 and May 2017; 10 World Congress on Brain Injury in April 2017; International Neuropsychological Society Meeting February 2016 ,February 2017, February 2018 and February 2019; 8th Federal Interagency Conference June 2018, and American Psychological Association Conference August 2018.
- Study is closed for enrollment, last follow-up on 12/30/18. Data analysis has started.
- Preliminary results from 40 participants who completed the training indicate that at week 5, after GOALS training, but not after EDU training, participants significantly improved on neuropsychological measures of attention/executive function, complex functional task performance and measures of emotional regulation. Participants reported incorporating trained strategies into their daily lives.