Enhancement of PTSD Treatment With Computerized Executive Function Training

NCT #: NCT03260127

Date of IRB protocol: July 2022

Human Protocol (Version 1.41)

General Information

***Please enter the full title of your study::**

Enhancement of PTSD Treatment with Computerized Executive Function Training

***Please enter the Study Number you would like to use to reference the study:**

CPT plus EF Training
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

Add departments

and Specify Research Location:

Is Primary?	Department Name
◯	**VASDHS** - VASDHS

Assign key study personnel(KSP) access to the study

***Please add a Principal Investigator for the study:**

Crocker, Laura D., PhD

3.1 If applicable, please select the Research Staff personnel

A) Additional Investigators

Bomyea, Jessica A., PhD
Co-Investigator
Colvonen, Peter J., PhD
Co-Investigator
Jak, Amy J., PhD
Co-Investigator
Merritt, Victoria C., PhD
Co-Investigator
Norman, Sonya B., PhD
Co-Investigator

B) Research Support Staff

Davey, Delaney K.
Study Coordinator
Golshan, Shahrokh, PhD

Biostatistician
Higdon, Alexandra O., PsyD
Clinical Research Associate
Hoffman, Samantha N.
Clinical Research Associate
Jurick Lefler, Sarah, PhD
Post-Doc
Keller, Amber Victoria
Clinical Research Associate
Marvin, Morgan E., BA
Research Associate
Ory, Jillian Leigh, BA
Research Associate
Schierbeek, Jackson
Research Associate
Witten, Cody
Research Associate

***Please add a Study Contact**

Crocker, Laura D., PhD

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

VASDHS IRB
Human Subjects Protocol
v20190121

Section 1 - Preliminaries

Principal Investigator:

Laura D. Crocker, PhD

Protocol Title:

Enhancement of PTSD Treatment with Computerized Executive Function Training

IRB Protocol Number:

H170017

Protocol Nickname:

CPT plus EF Training

Form Template Version:

v20150115

Date Prepared:

07/26/2022

Please be advised that this protocol application form has changed as a result of the 2018 Common Rule. There are new questions and sections, and you may be required to provide additional information to previous sections.

1a) Is this study considered human research?

◉ Yes

○ No
○ I don't know

1b) Please select:

○ This is an application for a NEW human subject research protocol
◉ This is a revision of an existing protocol

Was this study initially approved prior to January 21, 2019?

◉ Yes ○ No

Were you instructed to convert to the 2018 Common Rule Requirements?

○ Yes ◉ No

Section 2 - Research Subjects

2a) What is the total planned number of VA-consented subjects?

Include the total number of subjects who will prospectively agree to participate in the study (e.g., documented consent, oral consent, or other).

200

2b) What is the total number of VA subjects who WILL NOT be consented?

Include the total number of subjects that will be included without consent (e.g., chart review). *Note: Data about people are still considered "human subjects" by the IRB, so even if you do not intend to contact the patients whose charts you will review, you still should enter the number of charts as your "planned subjects."*

0

Section 2.1 Consented Subject Groups

2.1) For each of the subject categories listed below, indicate whether or not these subject groups will participate in the study:

2.1a) Children under the age of 18
Note: If neonates or children will be involved in this study, certification by the Medical Center Director will be required. Only minimal risk research may be performed with children. Only non-invasive monitoring and/or prospective observational and retrospective record review studies that are minimal risk can be conducted in VA involving neonates.

○ Yes ◉ No

2.1b) Pregnant women

○ Yes ◉ No

2.1c) Individuals with cognitive/decisional impairment

○ Yes ◉ No

2.1d) Non-English-speaking individuals

○ Yes ◉ No

2.1e) Prisoners of War (explicitly targeting this group)

○ Yes ◉ No

2.1f) Non-Veterans (Note: Justification for inclusion of non-Veterans will be required)

○ Yes ◉ No

2.1g) Incarcerated individuals (Note: VA CRADO approval will be required)

○ Yes ◉ No

2.1h) VA employees - including VA paid, IPA, or WOC (Note: Union review and authorization may be required)

◉ Yes ○ No

2.1i) Students of the institution (e.g., resident trainees) or of the investigator

◉ Yes ○ No

2.1j) Patients with cancer (or high cancer risk) [explicitly targeting this group]

○ Yes ◉ No

Section 3 - Study Features (these items default to "No" for convenience)

3) This section consists of several Yes/No questions addressing protocol characteristics. Click on *Save and Continue*.

Section 3.1 Protocol Basics

Select all that apply

3.1a) The research **intends to change** the participant.

◉ Yes ○ No

3.1b) **Interactions** with living participants to collect data or specimens with no intent to change them.

○ Yes ◉ No

3.1c) This is a study that **never** has any **subject contact and does not collect subject identifiers**

○ Yes ◉ No

3.1d) This is a **chart review** study involving retrospective or prospective medical records.

○ Yes ◉ No

3.1e) This is a **multi-site** study occurring in-part or in-full at other locations.

○ Yes ◉ No

3.1f) There is an **international** component to this research. *International research includes sending or receiving human derived data or specimens (identifiable, limited data set, coded, or deidentified) to or from an international source. International research does not include studies in which VA is only one of multiple participating sites where the overall study-wide PI is not a VA investigator.*

○ Yes ◉ No

3.1g) This study includes **off-station activity** (not including VA-leased space or CBOC clinics) conducted under VASDHS IRB approval. *Note: this does not include research conducted by a collaborator at their home institution under their institutional approval.*

◉ Yes ○ No

3.1h) VA subjects will **participate** in part or in full **at other locations** (not including VA-leased space or clinics) under VASDHS IRB approval. *Note: if this study involves remote participation of subjects, please indicate "no" and describe their remote participation in section 9 of the application. This question is intended to understand whether participants must physically go to a non-VA location to participate in this VA research study.*

◉ Yes ○ No

Section 3.2 Specimen Use and Data Repository

Indicate whether or not each of the following applies to this protocol

3.2a) Involves specimens that are left over from pathological or diagnostic testing (**non-research specimens**)

○ Yes ◉ No

3.2b) Involves **specimens collected for research** purposes **only**

○ Yes ◉ No

3.2c) This study includes **specimen banking** (specimens are retained for use outside of the purposes of this protocol)

○ Yes ◉ No

3.2d) The study involves **DNA** genotyping or other **genetic analysis**

○ Yes ◉ No

3.2e) Biological **specimens/material** will be sent outside of the VA.

○ Yes ◉ No

3.2f) A **data repository** is maintained (data are retained after completion of the protocol for other uses, IMPORTANT: see **?** before checking "yes")

○ Yes ◉ No

3.2g) **Data will be shared outside** of the VA (identifiable, coded, limited data set, or deidentified)

◉ Yes ○ No

Section 3.3 Treatment and Clinical Trials

Indicate whether or not each of the following applies to this protocol

3.3a) Includes a **treatment** component (a research treatment)

◉ Yes ○ No

3.3b) Study is a **clinical trial.** *Note: A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.*

◉ Yes ○ No

3.3c) Has a data safety monitoring board (**DSMB)** or data safety monitoring committee.

○ Yes ◉ No

3.3d) Has a **data safety monitoring plan** (but not a DSMB) (this is not the data security plan, it is a safety plan).

◉ Yes ○ No

Section 3.4 Drugs and Devices

Indicate whether or not each of the following applies to this protocol

3.4a) **Drugs** that require **FDA** action such as an Investigational New Drug (IND) approval or exemption or 510 (k) approval.

○ Yes ◉ No

3.4b) Other drugs, supplement, etc. that **do not require FDA** action for inclusion in the study.

○ Yes ◉ No

3.4c) Medical **devices requiring FDA** IDE approval or waiver

○ Yes ◉ No

3.4d) **Other** medical **devices**

○ Yes ◉ No

Section 3.5 Risk and Hazards

Indicate whether or not each of the following applies to this protocol

3.5a) Study places subjects at **greater than minimal risk** (do not include risks that are due to standard care)

◉ Yes ○ No

3.5b) Human subjects are exposed to **radioisotopes** (do not include standard care).

○ Yes ◉ No

3.5c) Subjects have other **radiation exposure** (e.g., x-rays) (do not include standard clinical use).

○ Yes ◉ No

3.5d) Target population has psychiatric diagnosis or behavioral complaint.

◉ Yes ○ No

Section 3.6 Clinical Facilities and Standard Care

Indicate whether or not each of the following applies to this protocol

3.6a) Study **uses VA clinical services** (e.g., adds required tests run in the VA lab for study purposes; research procedures concurrent with clinical care)

○ Yes ◉ No

3.6b) Includes procedures or drugs that will be considered **part of standard care.**

◉ Yes ○ No

3.6c) Involves **lab tests done for research** purposes.

○ Yes ◉ No

Section 3.7 Subject Expenses and Compensation

Indicate whether or not each of the following applies to this protocol

3.7a) There may be expense or added **costs to the subject** or the subject's insurance.

○ Yes ◉ No

3.7b) This is a **qualifying cancer treatment trial** and subjects may be billed for study drugs or procedures.

○ Yes ◉ No

3.7c) This is a cancer treatment trial but **subjects will not be billed** for study drugs or procedures.

○ Yes ◉ No

3.7d) Subjects will be **compensated** (either in cash or other means such as a gift certificate).

◉ Yes ○ No

Section 3.8 Subject Activities

Indicate whether or not each of the following applies to this protocol

3.8a) Involves **surveys or questionnaires** completed by subjects

◉ Yes ○ No

3.8b) Includes the use of **recruitment materials** such as flyers, advertisements, or letters

◉ Yes ○ No

3.8c) Involves facial **photographs** or audio or video **recordings** of **patients**

◉ Yes ○ No

Section 3.9 Sponsors and Collaboration

Indicate whether or not each of the following applies to this protocol

3.9a) This research is a funded research project **(commercial (industry) sponsor, NIH, VA, other).**

○ Yes ◉ No

3.9b) Other **commercial (industry) non-financial support** is provided (e.g., drugs or supplies).

○ Yes ◉ No

3.9d) The protocol has **Department of Defense** involvement (e.g., subjects or funding).

○ Yes ◉ No

3.9c) The PI or other study staff member has a financial interest or other **real or potential conflict** related to this study.

○ Yes ◉ No

3.9e) This study involves **collaborative** research activities (research conducted at other institutions under the authorities or approvals of the other institution/s). *Note: this may include other VA and/or non-VA institutions, but does not include off-site VA research.*

○ Yes ◉ No

Section 4 - Estimated Duration

4) What is the estimated duration of the entire study? (From IRB approval to IRB closure)

6 years

Section 5 - Lay Language Summary

5) Provide a summary or synopsis of the proposed study using non-technical language (not more than 1

paragraph)

This study focuses on helping Iraq and Afghanistan Veterans with posttraumatic stress disorder (PTSD) benefit fully from treatment. Although some people are able to successfully complete therapy and see significant improvements in symptoms, many others drop out of therapy early and/or do not notice improvements in symptoms. In addition to emotional symptoms, PTSD has been associated with thinking problems, including difficulty planning/organizing, thinking flexibly, and inhibiting distracting emotional information. One of the most effective treatments for PTSD - Cognitive Processing Therapy (CPT) - relies heavily on these types of thinking abilities to learn and use the skills that aid in recovery, thus having problems thinking likely contributes to high rates of dropout from treatment and/or problems fully engaging in treatment in order to get the most benefit from it. There is some evidence that computerized training programs are helpful for improving thinking, including planning/organizing, thinking flexibly, and inhibiting distracting information. Thus, it is possible that Iraq and Afghanistan Veterans may be better able to benefit from PTSD treatment if they first engage in computerized cognitive training to enhance their thinking abilities. Therefore, this study tests whether computerized cognitive training will in fact improve individuals' abilities to plan/organize, think flexibly, and inhibit distracting information and if this will in turn improve PTSD treatment outcomes and lead to more individuals completing treatment and showing greater improvements in emotional symptoms than CPT (when paired with a placebo word training condition).

Section 6 - Specific Aims

6) Provide a statement of specific aims and hypotheses that serve as the basis for this protocol. Emphasize those aspects that justify the use of human subjects.

Aim 1: Investigate whether Computerized Executive Function Training (CEFT) leads to objective and subjective improvements in executive functioning and whether this in turn mediates PTSD symptom improvement.

Hypothesis 1a: CEFT will be associated with improvements in both objective and subjective executive functioning.

Hypothesis 1b: Enhanced executive functioning will mediate the relationship between treatment group and PTSD symptom improvement.

Aim 2: Investigate the efficacy of administering CEFT prior to Cognitive Processing Therapy (CEF-CPT) in improving treatment adherence, completion rates, and outcomes in OEF/OIF Veterans with PTSD.

Hypothesis 2a: Individuals in the CEFT-CPT condition will have greater improvements in PTSD symptoms and quality of life than the control condition (placebo word training plus CPT).

Hypothesis 2b: Individuals in the CEFT-CPT condition will have higher rates of treatment engagement (i.e., completing more hours of homework and attending a greater number of sessions) and higher rates of treatment completion than those in the control condition.

Aim 3: Investigate whether functioning of brain regions in an EF network at baseline predicts treatment response.

Hypothesis 3: Dysfunction in a network of brain regions supporting EF will predict poorer response to treatment. Specifically, those who do not complete treatment and who demonstrate a poorer response will exhibit decreased connectivity between dorsolateral PFC and other regions, including anterior cingulate cortex and parietal cortex, compared to completers and better responders.

Section 7 - Background and Significance

7) Provide a succinct discussion of relevant background information to justify performing the proposed study.

PTSD affects approximately 14% of OEF/OIF Veterans and leads to considerable personal and societal costs (e.g., increased morbidity, reduced work productivity, poorer relationships). Cognitive behavioral therapy (CBT) has been shown to be one of the most effective treatments for PTSD. The Institute of Medicine

and VA/DoD Clinical Practice Guidelines for PTSD recommended two types of trauma-focused CBTs in particular as frontline psychotherapies for PTSD: cognitive processing therapy (CPT) and prolonged exposure (PE). These evidence-based CBTs can improve PTSD symptoms, enhance quality of life, and save billions of dollars by improving occupational, social, and physical health functioning. Despite significant efforts by the VA to make evidence-based treatments readily available to Veterans with PTSD, a substantial portion (approximately 50%) of individuals drop out of treatment prematurely, do not respond to treatment, or relapse after treatment completion. Treatment engagement is worse for OEF/OIF Veterans, who are less likely to begin evidence-based treatment, attend fewer sessions, have higher dropout rates, and are less likely to complete treatment than civilians and Veterans from other eras.

One likely barrier to treatment engagement and effectiveness is the executive functioning problems present in individuals with PTSD. Executive functions (EFs) are the set of higher-level cognitive skills (e.g., problem solving, set-shifting, cognitive flexibility) that organize and integrate lower-level cognitive processes in order to perform complex, goal-directed tasks. PTSD has been associated with EF deficits, including impairments in inhibitory control, working memory, and cognitive flexibly, as well as dysfunction in a network of brain regions that support EFs (e.g., prefrontal cortex [PFC], cingulate). PTSD not only disrupts the functioning of PFC during EF tasks but also its functional communication with other regions, preventing the downregulation of limbic regions by PFC when faced with perceived threats and preventing PFC from effectively modulating parietal cortex to ignore emotional distraction and maintain task goals.

EFs are essential for CBT in order to engage the cognitive skills involved in treatment (e.g., self-monitoring, inhibiting distorted thoughts, flexibly generating/evaluating alternative thoughts). This is particularly true for CBT approaches that are primarily cognitive in nature such as CPT, which involves identifying and challenging maladaptive trauma-related thoughts to alter their impact on emotions and behavior. Thus, EF deficits may lead to reduced CPT engagement and responsivity. In fact, worse EF at baseline has been associated with poorer response to CBT in several disorders (e.g., generalized anxiety disorder, obsessive compulsive disorder, schizophrenia). Further, a study of brain functioning during an EF task demonstrated that dysfunction in EF-related brain regions including PFC and cingulate cortex at baseline predicted nonresponse to CBT for PTSD.

Many researchers have argued that using methods that more directly target the dysfunctional cognitive processes present in various psychological disorders will improve current treatment approaches. Therefore, directly targeting EF prior to CPT via cognitive training would strengthen executive networks and likely boost treatment effectiveness, allowing Veterans to fully engage in and benefit more from components of CPT (e.g., cognitive restructuring). Research indicates that cognitive training can improve EF and enhance functioning in EF-related regions including PFC and parietal cortex. Cognitive training has been implemented as an intervention for various psychiatric conditions, including schizophrenia, ADHD, anxiety, depression, and substance abuse with evidence that it improves cognitive processes, clinical symptoms, quality of life, and adaptive functioning. Importantly, studies of PTSD that used computerized training to enhance attentional /cognitive control found that it reduced PTSD symptoms. In addition, computerized attention bias modification (ABM) training has been used in individuals with PTSD to facilitate disengagement of attention from negative /threatening information. Although ABM training was not designed to target EF per se, research indicates that ABM improves PFC functioning and its communication with other brain regions, suggesting it enhances top-down attentional control. Two studies that used ABM to augment CBT indicated that this combination was associated with a greater reduction in PTSD and anxiety symptoms after treatment compared to a control condition. Additional evidence that EF training is likely a useful adjunct to trauma-focused therapy for PTSD comes from research showing that it can increase mental health treatment completion rates and enhance response to CBT in other psychiatric conditions.

Thus, the main goal of the proposed study is to examine whether administering computerized EF training (CEFT) immediately prior to CPT will improve executive functioning and enhance treatment adherence, completion rates, and psychological and functional outcomes in OEF/OIF Veterans with PTSD. Objective (neuropsychological) and subjective (self-report) measures of EF will be collected to determine if CEFT enhances EF and if this in turn mediates the relationship between treatment condition and PTSD symptom improvement. Functional neuroimaging during EF tasks will also be collected at baseline to determine whether functioning within an EF network predicts treatment response, above and beyond traditional paper-and-pencil measures of EF.

The proposed research aims to reduce barriers to treatment engagement and has potential to significantly enhance current treatments for PTSD by combining cognitive and psychotherapeutic approaches. T argeting EF directly and independently represents a logical, innovative, and empirically-informed method for augmenting existing treatments for PTSD in order to optimize outcomes. Findings from the study will not only directly inform clinical practice, but also have the potential to significantly reduce societal costs and burden, improve access to care, and reveal ways to better match individuals with treatments they are most likely to benefit from. Successful treatment of PTSD also reduces comorbidities including depression, substance use, and suicidality and improves the quality of Veterans' lives, including enhancing physical health, employment rates/work productivity, and interpersonal functioning.

Section 9 - Design and Methods

9) Describe the research design and the procedures to be used to accomplish the specific aims of the project. Provide a precise description of the planned data collection (include what systems or databases will be used/accessed to gather data), analysis and interpretation. For chart review studies, include the timeframe

of collection. Address sample size, inclusion of women and minorities. Define in clear terms exactly what will be done to the human subjects.

Overview: The study is a randomized controlled trial (RCT) that will compare computerized EF training administered prior to CPT (CEFT-CPT) to a placebo word game training prior to CPT (WT-CPT). Goals of the research include 1) examining whether CEFT improves EF in OEF/OIF Veterans with PTSD and whether this in turn mediates PTSD symptom improvements, 2) investigating the efficacy of CEFT-CPT in improving treatment adherence, completion rates, and psychological and functional outcomes, and 3) determining whether baseline measures of EF predict treatment response. Veterans will be enrolled from the VASDHS system of PTSD clinics, spanning the main and 3 satellite facilities, and general outpatient mental health clinics. Assessments will be administered at baseline, immediately after CEFT or word training (prior to CPT), and after CPT completion.

Participants:

Inclusion criteria: 1) OEF/OIF Veterans enrolled at VASDHS, 2) aged 18-55 3) current PTSD diagnosis, 4) endorsement of cognitive complaints, 5) no pending medication changes, 6) English-speaking. Given the potential impact on outcome variables of interest, we will track current medication use in enrolled Veterans to ensure no recent or pending changes.

Exclusion criteria: 1) active substance use disorder in the last month, 2) suicidal intent or attempt within the last month, 3) schizophrenia, psychotic disorder and/or bipolar disorder, 4) dementia, 5) premorbid IQ < 70, 6) participation in other concurrent PTSD intervention studies, 7) previous completion of more than 4 CPT sessions, 8) history of a documented neurological disorder (e.g., Parkinson's disease, multiple sclerosis, epilepsy) 9) moderate to severe TBI (loss of consciousness greater than 30 minutes or post-traumatic amnesia greater than 24 hours).

Further exclusion criteria details: A history of mild TBI is highly comorbid in OEF/OIF but the majority of the literature supports a mental health etiology to persistent symptoms following mTBI; the current study will account statistically for mTBI history but it is not exclusionary.

Since the primary aim of the present research proposal is centered around the intervention component, Veterans will still be enrolled in the study if they have contraindications for MRI, since that will not prevent them from engaging in and completing PTSD treatment in real-world settings. In addition, the rate of exclusion for MRI-contraindications is very low. Contraindications for MRI include: pregnancy, cardiac pacemaker, metal fragments in eyes/body, participants who have been a metal worker/welder, aortic aneurysm clips, prosthesis, by-pass surgery/coronary artery clips, hearing aid, heart valve replacement, IUD, a shunt (ventricular or spinal), electrodes, metal plates/pins/screws/wires, or neuro/bio-stimulators (TENS unit), vision problems uncorrectable with lenses, claustrophobia, inability to lie still on one's back for approximately 60 minutes, prior neurosurgery, older tattoos with metal dyes, unwillingness to remove nose, ear or face jewelry, braces or permanent dental retainers.

Subject recruitment: Veterans with PTSD will be recruited at VASDHS. We will utilize the VASDHS system of PTSD clinics, spanning the main and 3 satellite facilities, and general outpatient mental health clinics. An effort will be made to recruit women and minorities into the study. Staff in each clinic will provide a descriptive study flyer to patients newly accepted and enrolled into the outpatient PTSD program with a diagnosis of PTSD (based on information collected through intake). Individuals reporting interest in the study will be asked for verbal consent to be contacted by the research coordinator. In addition, informational flyers will be posted throughout the clinics with telephone number listed for interested participants to call. Research databases of Veterans who have previously consented to be contacted about additional study opportunities can also serve as a recruitment tool. The research coordinator will contact prospective participants to provide an explanation of study procedures and to complete a phone-based screening. A lab-based baseline assessment visit will be scheduled if the individual meets basic eligibility requirements.

During recruitment, we will initially screen Veterans by phone. Those that are eligible for the study based on the phone screen will be brought to the lab for consenting, intake, and baseline assessments (approximately 200 Veterans). However, we assume a portion of those individuals will not qualify for the study. That will leave us with approximately 150 Veterans (75 per condition) to randomize to treatment. For recruitment, we will utilize the VASDHS system of PTSD clinics, spanning the main and 3 satellite facilities, and general outpatient mental health clinics. VA employees are not the target population, however they will not be excluded if they meet the inclusion criteria.

Financial Incentives: Participants will be compensated for their time after each completed assessment. Veterans will receive $50 for the baseline assessment ($30 for completion of the questionnaires and

neuropsychological assessment, $20 for the fMRI assessment), $30 as a bonus for completing at least 80% of the cognitive training (or placebo word games), $50 for the post-computerized training assessment, and $70 for the post-therapy assessment (Total possible = $200).

Procedures:

Design and methods: Veterans will be randomized to either 12 weeks of CEFT-CPT or placebo word training plus CPT. Assessments will be administered three times: at baseline, immediately after CEFT or word training (prior to CPT), and after CPT completion. Assessment of PTSD diagnosis, symptom severity, quality of life, and subjective and objective measures of cognition will be administered at baseline (prior to computerized training onset), immediately after completing the cognitive training portion of the study (i.e., 6 weeks after baseline, just prior to starting CPT), and after completion of CPT treatment (approximately 6 weeks later, a total of 12 weeks after study initiation). Treatment satisfaction will be assessed after CEFT and CPT completion. Symptom severity will also be assessed at the midway point for the cognitive training and weekly during the CPT intervention component. Functional neuroimaging during rest and during two well-validated EF tasks will be collected at baseline, a Go-No Go Task that taps inhibition and an N-Back Task that taps working memory.

Pre-study screening (15-30 minutes): Initial screening for interest and eligibility will take place in person or via telephone. Veterans will be given an overview of the study and, after providing verbal consent, will be screened with a questionnaire covering the major inclusion/exclusion criteria. Veterans who are not excluded based on the phone screening and who express interest in participating in the study will be invited to come to the VASDHS for continued evaluation of eligibility for participation in the study.

Baseline Assessment (4 hours): During the baseline appointment, Veterans will first provide written informed consent and HIPAA consent and then complete a structured clinical interview, the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) to determine PTSD diagnosis. Veterans will be then be assessed on a battery of self-report questionnaires to measure psychiatric symptoms and functioning including PTSD, depression, quality of life, and subjective EF in daily life (see measures section below). Objective cognitive functioning will be measured with standard neuropsychological tests in the domains of EF, verbal memory, attention/processing speed, and premorbid intellectual functioning. Multiple measures of EF will be administered that include tests of inhibition, working memory, and cognitive flexibility. The other cognitive domains assessed have also been associated with PTSD and may contribute to poorer EF (e.g., processing speed). Objective measures of effort will also be administered to assess validity of neuropsychological testing, in order to accurately interpret test scores/performances. All assessments will be administered by a trained research assistant.

Veterans who meet MRI safety criteria will also attend a separate 1-hour MRI appointment to collect functional neuroimaging data during two well-validated EF tasks. During this appointment, structural imaging data will also be collected for registration to the functional data. If Veterans do not meet MRI safety criteria, they will perform the two EF tasks during the baseline assessment appointment, as data from the behavioral tasks will still be analyzed even if the fMRI data is not available.

Treatment Randomization: Following baseline assessment, participants will be randomized to the experimental (CEFT-CPT) or control condition (WT-CPT). A computer-generated randomization sequence will be provided by our statistical expert Dr. Shahrokh Golshan (consultant). Randomization will be stratified by gender to ensure a balanced number of males and females are in each treatment group. Participants, the study assessor, and therapists will be blinded to the experimental treatment condition.

Post-Intervention Assessments (3-4 hours): The full battery of self-report questionnaires measuring psychiatric symptoms, quality of life, and subjective cognitive functioning, objective measures of neuropsychological functioning, and structured clinical interview for PTSD diagnosis will be re-administered twice, once after cognitive training completion and again after CPT completion. For the neuropsychological tests, alternate forms will be used where available and the RCT design will distribute any practice effects equally across the two groups. Participants will also complete the two EF tasks again that were administered at baseline during neuroimaging (though fMRI will not be collected again) or during the baseline assessment if they did not undergo fMRI for safety reasons.

Assessment Measures:

Symptom Measures:

- **PTSD**: The Clinician-Administered PTSD Scale DSM 5 (CAPS-5; Weathers et al., 2013) is the gold-standard, semi-structured interview that corresponds to DSM-5 criteria for PTSD. The CAPS-5 shows strong reliability and validity.

  PTSD Checklist for DSM-5 (PCL-5; Weathers, Litz, Keane, Palmieri, Marx, & Schnurr, 2013) will be used to regularly assess PTSD symptomatology at several points throughout the study. The PCL-5 is a 20-item self-report measure of PTSD symptoms with good psychometric properties. The PCL-5 maps directly onto DSM-5 diagnostic criteria.

- **Depression**: Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) is a 21-question multiple-choice self-report inventory, one of the most widely used instruments for measuring depressive symptoms.
- **Subjective day-to-day executive functioning**: Behavior Rating Inventory of Executive Function (BRIEF; Guy et al., 2004) is an ecologically sensitive 75-item self-report questionnaire that measures several aspects of EF in an individual's everyday life in the last month, including inhibition, shifting, working memory, planning/organizing, emotional control, etc.

Optional measure: If there is any ambiguity in terms of psychiatric diagnoses based on the phone screen and a review of patient records (CPRS) that would disqualify the participant (i.e., schizophrenia, psychotic disorder, bipolar disorder, substance use disorder), the relevant portions of the MINI International Neuropsychiatric Interview (MINI; Sheehan, 2014) will be administered during the baseline assessment to clarify eligibility.

Objective neuropsychological testing: .

- **Tests of executive functioning**: Measures of inhibition, shifting/cognitive flexibility, and working memory include the Wisconsin Card Sorting Test (WCST; Heaton, 1981), Delis Kaplan Executive Function System (D-KEFS) Color-Word Interference Test and Trail Making Test (Delis, Kaplan, & Kramer, 2001), Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977)
- **Verbal memory**: California Verbal Learning Test-II (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000)
- **Tests of attention and processing speed**: Wechsler Adult Intelligence Scale – IV (WAIS-IV) Digit Span, Digit Symbol, and Symbol Search subtests (Wechsler, 2008)
- **Premorbid intellectual functioning**: Wide Range Achievement Test, Fifth Edition (WRAT5) Reading subtest (Wilkinson & Robertson, 2017) [administered only at the baseline visit]
- **Tests of neuropsychological performance validity**: Test of Memory Malingering (Tombaugh, 1996) and an embedded measure within the CVLT-II (i.e., Forced Choice)

Other measures:

- **Quality of Life**: World Health Organization Quality of Life-BREF (WHOQOL-BREF; the WHOQOL Group, 1998) comprises 26 items, which measure the following broad domains: physical health, psychological health, social relationships, and environment.
- **Functional Impairment/Disability:** Inventory of Psychosocial Functioning (IPF; Rodriguez et al., 2012) is a self-report measure that assesses PTSD-related functional impairment across several domains, including relationships, work, education, self-care, etc.
- **TBI History:** Ohio State University TBI Identificanion Method - Interview Form (OSU TBI-ID; Corrigan & Bogner, 2007) is a short, structured interview that assesses TBI history and details about injury including cause, presence/minutes of loss of consciousness and post-traumatic amnesia, number of TBIs, etc. [administered only at the baseline visit]
- **Client Satisfaction with Treatment:** Client Satisfaction Questionnaire (CSQ; Attkisson & Zwick, 1982) is an 8-item self-report scale measuring satisfaction with treatment. It has excellent internal consistency and correlates with therapists' estimates of client satisfaction. This instrument will be used to measure participants' satisfaction with the interventions.
- **Homework Compliance:** Homework Compliance Scale (HCS; Primakoff et al., 1986) is a single item questionnaire in which participants rate their degree of homework compliance on a scale from 0 (homework was not assigned) to 6 (I did more of the assigned homework than requested). An estimate of the number of minutes spent completing homework since the previous session and number of completed worksheets and assignments will also be recorded at each CPT session.
- **Alcohol Screening Tool:** The Alcohol Use Disorders Identification Test-C (Audit-C; Saunder et al., 1993) is a 3-item screening measure used to screen for alcohol use disorder, which is an exclusion criteria for the study.

Neuroimaging: Collected only at baseline

Experimental fMRI Tasks:

N-Back Working Memory Task: In this task, pseudo-words are presented on each trial and the participant must determine whether the current stimulus matches the one n-back. There are 3 types of n-backs in the task: 1-back, 2-back, and 3-back. Participants respond via a keystroke whenever they see a pseudo-word repeated either one, two, or three pseudo-words back. Each participant will receive a practice block before going into the scanner and two blocks while in the scanner, with each block containing all 3 N-back conditions in an alternating order. Reaction time and accuracy on each trial are recorded during scanning.

Go-No Go Inhibition Task: In this task, shapes are presented on screen. Participants are instructed to make a button press to every shape except when a circle or square appears on screen. Each participant will receive a practice block before going into the scanner and two blocks while in the scanner. Reaction time and accuracy on each trial are recorded during scanning.

Acquisition of images: All scans will be collected on a research-dedicated 3T General Electric (GE) Discovery MR750 whole body system using a 32-channel receiver coil (Nova Medical Inc, Wilmington MA). An initial localizer scan will be acquired to assure proper positioning in the scanner and to allow for slice prescription. An anatomical scan will be collected for registration of functional data to standard space. Blood oxygenation level dependent (BOLD) signal will be measured using gradient echo planar imaging during the functional tasks. In addition, two field maps will be collected to assist with distortion correction of the BOLD images.

Resting state: Resting state data will be acquired for 8 minutes via T2-weighted functional images using a gradient-echo multiband echoplanar imaging method. Participants will be instructed to remain still, stay awake, keep their eyes open, and focus on a fixation point.

Computerized EF Training: CEFT will consist of 6 weeks of online training 30 minutes a day for 5 days a week on a home computer followed by the standard protocol of the cognitive-only version of CPT (CPT-C) for 6 weeks (2 sessions per week). CEFT will be administered via BrainHQ by Posit Science and will consist of six cognitive training modules that target executive processes of inhibition, shifting, and updating of working memory. All tasks become more challenging with practice. Veterans will receive a brief introduction to the program on site at the VA (log-in, which modules to complete, and how long to spend each day on the training). These instructions will be provided in a written format to be used once participants are on their home computer. If participants do not have a home computer/internet access, they can complete the modules at another location such as a public library or at the VA, but training will still be self-directed. BrainHQ offers a secure portal that allows for monitoring of usage and progress of participants. Researchers will be in weekly phone contact with participants to check on their progress with the cognitive training and answer any questions. This check-in will also serve the purpose of keeping them engaged and motivated.

BrainHQ Modules:

1. Mind Bender: cognitive flexibility/set shifting exercise, participants switch between two different rules in order to make correct responses
2. Auditory Ace: auditory working memory exercise, essentially an N back task where auditory information is retained and manipulated to determine if the current card matches a card N steps back in the sequence
3. Card Shark: visuospatial working memory exercise, similar to the Auditory Ace, except the information used to determine matches is presented visually
4. Juggle Factory: visuospatial working memory exercise, participants reconstruct a sequence of numbers in moving circles in the correct order, at more difficult levels participants must inhibit the influence of distracters
5. Mixed Signals: inhibition exercise, participants respond if what they hear and see matches in a particular way (while ignoring irrelevant information), otherwise they withhold their response
6. Divided Attention: inhibition exercise, participants indicate whether two objects match on a particular aspect (e.g., shape, color, fill) while ignoring irrelevant/competing aspects

Placebo word games: Participants in the active control group will be assigned to complete computerized placebo game training at the same frequency as CEFT. *Games and puzzles will be accessed online via BrainHQ in a similar manner to the CEFT condition.* This placebo condition controls for the effects of computer exposure, contact with research staff, and monetary payments. In addition, it controls for nonspecific engagement and motivation through the reinforcement of graphics-based computer games but does not provide the constrained, intensive, adaptive training of specific executive functions that the active condition provides. Participants will rotate through a series of games (e.g., *sudoku, crossword, connect four*) for the same number of hours as the EF training condition. After 6 weeks of game training, they will also receive CPT-C as detailed below.

Cognitive Processing Therapy: CPT is an evidence-based, trauma-focused therapy for PTSD endorsed by the VA/DoD Practice Guidelines and is widely available within VASDHS. Patients will receive a well-validated version of CPT, CPT-Cognitive only (CPT-C), which is a standard PTSD treatment provided at the VA that differs from the original version of CPT in that it does not include written trauma accounts. It entails 12 visits to the VA, each lasting 50 minutes.

More specifically, CPT-C is a form of CBT targeting PTSD and other corollary symptoms following traumatic events that has been used successfully with patients exposed to a range of other traumatic events, including combat trauma. Based on a social cognitive theory of PTSD and trauma, CPT focuses on the content of trauma-related thoughts, whether these thoughts are consistent or inconsistent with the patient's prior beliefs about the world, and the impact these thoughts have on emotions and behaviors. In the first session patients are educated about PTSD symptoms, cognitive theory, and treatment goals. The patient is given a practice assignment to write a one-page 'Impact Statement' focusing on how the identified traumatic experience has influenced thoughts and beliefs about the self, others, and the world. In the next two sessions the Impact Statement is used to identify distorted thoughts about the trauma ("stuck points") and the patient is taught to identify the

relationship between thoughts and feelings. Sessions 4 and 5 focus on helping the patient identify and challenge distorted cognitions. Sessions 6–12 focus on teaching and reinforcing cognitive behavioral therapy skills, with a specific emphasis on the themes of trust, safety, power, control, self-esteem, and intimacy.

Veterans who meet the screening requirements who prefer to be seen at the Mission Valley Clinic will be given the opportunity to complete therapist meetings at that facility. Study staff will meet with the patient and conduct study procedures in the same manner in which they are conducted in the San Diego VA.

Therapy appointments will be offered via VA Video Connect if participants are unable to attend an appointment in person. Questionnaires given at psychotherapy sessions (PCL-5 and HCS) can be delivered via telehealth with providers working remotely.

Data Analysis: Data management and analysis will be supervised by Dr. Golshan (Biostatistician and consultant). Data will be analyzed from all randomized subjects on whom we have a baseline assessment and at least one post-baseline evaluation. Every attempt will be made to obtain at least one follow up assessment on any individuals who drop out of treatment. Data will be screened for outliers, missing values, and violation of statistical assumptions. Preliminary analyses will be used to examine the descriptive statistics of the study sample and assess for the influence of outliers and non-normally distributed variables for possible exclusion or transformation. Gender, age, medications, depression, and TBI-related variables will be examined for differences between groups at baseline; they will be added as covariates if differences are significant.

Missing Data: Missing data values will be minimized by intensive training of the staff in techniques of clarifying answers and checking questionnaires while Veterans are on-site. When missing values are identified, several approaches to acquire the necessary data will be employed including 1) contacting the Veterans to obtain the missing data and/or 2) examining the missing data to assess randomness. We expect missing data to be randomly distributed. Missing data (i.e., loss to follow up) will be tested to determine if it is informative, and the methods developed by Diggle (1989) and Ridout (1991) to test for completely random dropouts will be applied. We will test whether the drop-outs are random or systematic by comparing the drop-outs with the study completers on the baseline data. An absence of significant differences would support the random nature of drop-outs. If the extent of missing data is small and the data appear to be consistent with a missing-at-random model (MAR), then the maximum-likelihood analysis using all randomized cases and the observed data is an appropriate method for handling the missing data.

Analyses will be conducted using multilevel modeling (MLM; also known as hierarchical linear modeling and linear mixed effects modeling). MLM has several advantages over more traditional analytic approaches such as change scores or repeated measures ANOVAs, as it allows for the inclusion of participants who have missing data and who dropped out of the study prematurely without using data imputation or biased procedures that often reduce power, such as casewise deletion. MLM also accounts for the fact that repeated observations across time are not independent but are nested within individuals. This method can provide an estimate of the individual variability around the population trend, the variability of the individual intercepts (baseline symptom levels) and slopes (change in symptoms across time), and the correlation between them. Initial model testing will be conducted to determine whether including individual-level random effects of intercept and slope (to model variability in initial symptom level and variability in response to treatment) will improve model fit. In addition to including the significant random effects, the model will include the fixed effects of treatment group, time, and group-by-time interaction. Data will be analyzed from all randomized subjects (full intent-to-treat sample) using all available data collected at the different assessment points.

Image processing: All functional image processing will be done with the Analysis of Functional Neuroimages (AFNI) software package. AFNI will be used to first preprocess the data (motion corrected, fieldmap corrected, slice-time corrected, temporally filtered, spatially smoothed). For examination of regional activation for each task, a general linear model that includes a baseline and linear trend plus regressors for each trial type and parameters to account for any residual motion will be calculated. A map of the fit coefficient for the contrasts of interest for each task (i.e., the contrast between 2-back and 1-back conditions in the n-back task, the contrast between no go and go trials in the go-no go task), will be created for each subject. Functional connectivity analysis will be performed within AFNI via Context-Dependent Correlation Analysis (McLaren et al., 2012). This analysis enables account for the effect of a specific task contrast on the connectivity model in the analysis, and the interaction between this psychological effect (task contrast) and the neuronal response (physiological effect) at the seed region (dorsolateral prefrontal cortex, anterior cingulate cortex, and other regions activated by the specific task derived from main effects analysis). In other words, the integration process at multiple levels in the brain is dependent on the context of task conditions. Other than the seed time course, such a context-dependent correlation analysis, aka psychophysiological interaction (PPI), requires the insertion of one specific regressor in the model, a second-order regressor of the interaction. Additionally, the individual raw signal datasets will be band-pass filtered ($0.009 < f < 0.08$) to reduce physiological noise. Individual timecourses in these processed raw signal datasets will be extracted for seed regions of interest (ROIs). After censoring for data points >2

standard deviations from the average signal, hemodynamic delay from the seed voxel timecourse will be extracted. The resultant signal will then multiplied by the contrasts of interest thereby creating an interaction timecourse to be convolved with a gamma-variate hemodynamic function. The interaction timecourses will be used as regressors of interest together with nuisance regressors and AFNI's REML function will be applied. The resulting correlation coefficient for the timecourse in the regions of interest will be calculated for each voxel. Correlation maps for the timecourse in the regions of interest and the timecourse from all other brain voxels will be created to demonstrate. The Fisher Z transforms of these correlation maps will be warped to conform to the Talairach atlas and a Gaussian blur with a maximum of 6.0 mm full width at half maximum (FWHM) will be applied. Resting state data will be analyzed using well established methods in the field that Dr. Eyler has experience implementing, including regressing out sources of variance (e.g., motion, physiological noise, whole-brain global signal, cerebrospinal fluid and white matter signal; see methods of Dev et al., 2016; Nguyen et al., 2016). Network seeds will include task-positive regions involved in top-down attentional control (e.g., DLPFC, inferior parietal lobule [IPL]) and task-negative regions part of the default mode network (e.g., medial prefrontal cortex [mPFC] and posterior parietal cortex [PCC]; Fox et al., 2005). Freesurfer will be used to extract volumetric and cortical thickness data in ROIs (e.g., DLPFC, ACC) to be used in exploratory analyses of the structural data to complement the fMRI results.

COVID-19 Emergency Procedures: In order to ensure patient safety during the COVID-19 public health emergency, the temporary procedures detailed below allow for participation while maintaining social distancing. The protocol remains as approved with the following exceptions:

1. If a Veteran is potentially interested in participation after the initial contact and screens eligible via the telephone screen, we will send an encrypted email (using VA Azure RMS), a message through MyHealtheVet, documents by US mail, or a DocuSign envelope (see below for procedure) containing (1) the approved ICF, (2) the approved HIPAA document, and (3) the CA Experimental Subjects Bill of Rights, and arrange a telehealth visit through a VA-approved secure telehealth communication software to complete the informed consent process, explain the HIPAA Authorization, and CA Experimental Subjects Bill of Rights. The staff member will witness the signing of the ICF and HIPAA Authorization and will instruct the potential participant to provide documentation of written informed consent by either returning images of the documents or the full signed PDF through MyHealtheVet, by allowing a screenshot of the signed documents (approval date and signature must be clearly visible), or downloading the signed forms through DocuSign. These electronic documents will be stored electronically separate from study data on the R: drive and the participant will retain their copies.
2. If secure telehealth communication is not possible or available, consenting and HIPPA authorization will be conducted via phone after the participant receives the documents through the mail. The participant will be instructed to mail back the signed consent form. Paper documents will be stored securely according to VA requirements.
3. Once documentation of written consent is received, the staff member will begin the baseline eligibility assessment. Interview-based measures for assessments will be completed using a VA-approved secure telehealth communication software or phone in which a staff member will transcribe the responses into an electronic form behind the VA firewall or record the answers on paper forms that will be stored and locked in participant data files per usual protocol.
4. The participant may complete assessment questionnaires in the following ways: (1) complete the forms (on paper and scan or using a fillable pdf) and return them via MyHealtheVet, (2) complete the forms using a password-protected pdf sent to them via encrypted email (using VA Azure RMS) and returned via email to a staff VA email account, or (3) read responses to the items to a staff member who will record the responses into an electronic form behind the VA firewall on the R drive. If electronic methods prove difficult for a particular participant, paper packets will be returned to the VA by U.S. post or they may return them during their in-person abbreviated assessment and this decision will be documented. Questionnaire forms will not contain PIV and are identifiable only by participant ID.
5. Neuropsychological assessments will be completed using VA-approved secure telehealth communication software to the extent possible. If the software is not available due to technology issues, verbal neuropsychological measures will be delivered via phone. Shortened in-person visits will be scheduled in order to complete neuropsychological tests that are unable to be administered using telehealth communication software or phone. These visits will be abbreviated to minimize contact between staff and Veteran participants. Safety guidelines for these visits will be detailed in the RAMP plan and will be consistent with VA guidelines for the resumption of in-person human research.
6. If possible, MRI sessions will be scheduled immediately following the participant's in-person baseline visit to minimize the number of VA visits the Veteran participant will be required to make. Imaging appointments will follow all UCSD safety guidelines in addition to VA guidelines for the resumption of in-person human research.

7. To assess the impact of COVID-19 on participants, the CAIR Pandemic Impact Questionnaire (C-PIQ) will be administered during assessments using the methods described above.
8. Assessments (including telehealth/phone appointments, questionnaires, and the abbreviated in-person neuropsychological testing) will be administered at baseline, again after the cognitive training portion of the study, and post treatment.
9. All psychotherapy sessions will be delivered via telehealth using VA Video Connect. If VA Video Connect is not available due to technology issues, therapy will be delivered via other secure telehealth communication software or phone.
10. The study is currently recruiting and newly enrolling, according to guidelines set forth in the VA Interim Policy on Human Subject Research During the COVID-19 Pandemic and our IRB-approved RAMP plan.

The additional protocol for remotely consenting veterans using DocuSign is as follows:

1. At the time of remote consenting, the study team member/consenter will send a DocuSign envelope (email containing links to the study documents) to the potential subject.
2. At the scheduled time, the study team member (referred to as "consenter") will contact the potential subject via VA-approved secure telehealth communication software or phone. The consenter will guide the potential subject to open the DocuSign envelope (email) and the linked study documents therein. The consenter will open a copy of the study documents on their own computer as a reference. The consenter will review the study documents with the potential subject, ask questions to gauge comprehension, and answer any questions and concerns. If the potential subject agrees to participate in the study, the consenter will guide them to fill in the fields in the study documents (e.g., "Last, First, Middle Initial" name field, Last 4 SSN field, etc.) and to sign the documents. When the subject has signed the documents, they will click "FINISH" to finalize the documents.
3. While still on the telehealth communication software or phone with the subject, the consenter will receive an email notification to log into DocuSign. The consenter will verify that all fields are completed accurately and subsequently sign the document(s) (e.g., ICF). The consenter will guide the subject on how to download a copy(ies) of the signed document(s) to the subject's personal computer for their record.
4. The consenter will download a copy(ies) of the signed document(s) to a study folder in VA network drive (i.e., R:\Crocker) as study record.

Section 9.1 Clinical Procedures

9.1) Differentiate research procedures (or any procedures done for research purposes only) from clinical procedures (procedures that are done as part of standard care).

(Note: this differentiation should be clear in the consent form as well)

Research and usual care procedures: All procedures are done for research purposes. All study participants will receive Cognitive Processing Therapy (CPT) which is the standard of care for PTSD but will be delivered by study psychologist in the context of this research study.

Audio recordings of the therapy sessions that are conducted at the Mission Valley Clinic will be uploaded to the protected VA server for potential review by supervisors while onsite and deleted from the approved recorder so that no potentially identifying information is lost in transport.

In addition to the therapy conducted within this research study, Veterans will undergo an assessment battery that will be administered three times during the study – these assessments are also for research and not clinical purposes though the tests included in the assessment are standard clinical tools.

Section 9.8 Questionnaires & Surveys

9.8) Provide the name and a reference for questionnaires/surveys that are standard or identify them here and attach a copy of the questionnaire/survey. ***Questionnaires or surveys that are not clinical standard references must be uploaded. Reference the help link for additional information related to surveys administered to VA personnel and approved platforms for web-based surveys.***

1. Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2013)
2. PTSD Checklist for DSM-5 (PCL-5; Weathers, Litz, Keane, Palmieri, Marx, & Schnurr, 2013)

3. Beck Depression Inventory-II (BDI-II; Beck, Steer, &Brown, 1996)
4. Behavior Rating Inventory of Executive Function (BRIEF; Guy et al., 2004)
5. Wisconsin Card Sorting Test (Heaton, 1981)
6. Delis Kaplan Executive Function System, Color-Word Interference Test and Trail Making Test (Delis, Kaplan, & Kramer, 2001)
7. Paced Auditory Serial Addition Test (Gronwall, 1977)
8. California Verbal Learning Test-II (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000)
9. Wechsler Adult Intelligence Scale – IV (WAIS-IV) Digit Span, Digit Symbol, and Symbol Search subtests (Wechsler, 2008)
10. Wide Range Achievement Test, Fifth Edition (WRAT5; Wilkinson & Robertson, 2017)
11. Test of Memory Malingering (TOMM; Tombaugh, 1996)
12. World Health Organization Quality of Life-BREF (WHOQOL-BREF; the WHOQOL Group, 1998)
13. Inventory of Psychosocial Functioning (IPF; Rodriguez et al., 2012)
14. Ohio State University TBI Identification Method - Interview Form (OSU TBI-ID; Corrigan & Bogner, 2007)
15. Client Satisfaction Questionnaire (CSQ-8; Attkisson & Zwick, 1982)
16. Homework Compliance Scale (HCS; Primakoff et al., 1986)
17. MINI International Neuropsychiatric Interview (MINI; Sheehan, 2014)
18. The Alcohol Use Disorders Identification Test-C (Audit-C; Saunder et al., 1993)
19. CAIR Pandemic Impact Questionnaire (C-PIQ)

Section 9.9 Data Safety Monitoring Board or Plan

9.9) Provide a Data Safety Monitoring Plan (DSMP) or the details of a Data Safety Monitoring Board; if a written plan is available, attach a copy of the plan to the submission form.

Data will be de-identified and labeled with a code number that is unique to each patient in the study. All hard copy data will be stored in locked file cabinets in locked rooms in VASDHS Building 13, while all electronic data
will be stored in password-protected files in a limited access folder on the secure VA network drive. A key code that links participants with their coded identifier will be maintained by Dr. Crocker. This key code will be stored
separately from all other study data and available only to Dr. Crocker and her research coordinator. Any materials with protected health information (e.g., informed consents) will be stored in separate locked file
cabinets from de-identified, coded materials to ensure the security of patient privacy. All computerized cognitive testing data will also be de-identified and coded with only an ID number and thus will contain no
Protected Health Information (PHI). The coded computerized cognitive data will be stored on a FIPS 140 compliant server that is accessible to the research team and then transferred to a secure VA network for statistical analysis. All statistical transfer routines are inherently secure via their operating platform and they contain no patient names or personal data. Participant confidentiality will be protected to the extent provided by law. Sensitive information that might be disclosed in this study and would be subject to mandatory reporting includes information regarding child or elder abuse. Evidence of suicidality or homicidality may also be disclosed to appropriate mental health personnel or others to ensure the safety of all parties. Raw and electronic data will be stored in the VASDHS in accordance with current VA research guidelines.

In addition, the institution's IRB requires regular updates on the status of research projects, including the number of participants enrolled, adverse events or unanticipated problems, number of withdrawals from the project, complaints about the research, and any protocol changes. Any adverse events or unexpected study-related side effects will be reported immediately to the IRB.

Regarding the cognitive training that will be administered via BrainHQ, data transport and storage systems are HIPAA and FIPS-140 compliant. No personally identifiable information is mandatory to use the BrainHQ program. User names will be coded as anonymized, de-identified study numbers or otherwise de-identified. The only information created, transmitted, and stored by the program pertains to usage (e.g., how much training has been done) and progress (e.g., how much improvement has been calculated) that a user makes. IP addresses are not recorded to be in HIPAA compliance. Also, data will be downloaded from BrainHQ on a regular basis.

There is the possibility of an abnormal finding on the MRI scan. However, the MRI scans are not being done for clinical purposes, and the MRI scan procedure is not sufficient for the clinical diagnosis of a possible brain disorder. The purpose of this scan is not to diagnose abnormalities, but on rare occasions a finding is observed that might be clinically important. Should there be cause for concern, with the permission of the participant, this information will be forwarded to the primary care physician for follow-up.

Section 9.11 Pictures and Audio/Video Recordings of Patients

9.11) Describe the purpose of photographs (facial), or audio, or video recordings of patients. Describe whether the recordings will contain, or potentially contain, identifiers. ***Note: use of photographs or recordings must be covered in the informed consent process and documented consent documents (e.g., consent form, information sheets, telephone screen scripts).***

Audiorecordings are used to ensure the fidelity of the psychotherapy delivered by study therapists. Recordings will be made with a digital audio recording device.

Section 9.12 Off Station Activities

9.12) Describe each off-station activity including where it occurs, subject involvement, and any additional required protections. ***Note: if the off-station activity is being conducted under the approval authority of another institution, this is not VA offsite research and should be described as collaborative research effort. Please contact the HRPP office if you have any questions***

Computerized cognitive training will be completed on Veterans' home computers. If they do not have a home computer, they will be able to complete it at another location, such as a local library. As discussed previously, data transport and storage systems are HIPAA and FIPS-140 compliant. No personally identifiable information is mandatory to use the BrainHQ program. User names will be coded as anonymized, de-identified study numbers or otherwise de-identified. The only information created, transmitted, and stored by the program pertains to usage (e.g., how much training has been done) and progress (e.g., how much improvement has been calculated) that a user makes. IP addresses are not recorded to be in HIPAA compliance. Also, data will be downloaded from BrainHQ on a regular basis.

MRI scanning sessions will be completed at the University of California, San Diego UCSD Center for Functional MRI (UCSD CFMRI). Before entering the scanning room, subjects will be screened for scan safety and will be inspected with a metal detector wand for potential metal on their body.

Off-station activity will only occur as part of COVID-19 emergency procedures to eliminate the need for participants to travel to the San Diego VA hospital for study treatment and assessment delivery. This will involve video teleconference into a participant's home. The clinician and assessor will be located at a VASDHS space at the time of the appointment unless staff are approved to telework or quarantined, in which case they will deliver the telehealth session through remote access or a VA-issued laptop. If VA-approved secure telehealth communication software is not working, the phone will be used. No additional protections are needed. Assessors and therapists will use telemental health services, or telephone, to contact and coordinate patient care and participant interest.

Section 10 - Human Subjects

10) Describe the characteristics of the proposed subject population. Include age, gender, ethnicity, and health status as appropriate. ***Note: Data about people are still considered "human subjects" by the IRB, so even if you do not intend to contact the patients whose charts you will review, you still describe the characteristics related to the subjects whose charts you will review.***

- **Provide inclusion and exclusion criteria as appropriate. Provide a statement how non pregnancy is confirmed if pregnancy is an exclusion criteria.**
- **For multisite studies, provide the total number of subjects from all sites and include description of the local site's role as a coordinating center if applicable.**
- **Indicate the number of VA participants to be studied.**
- **Indicate the estimated number of consented subjects that will fail the screening process, if any.**

Participants: The study specifically targets Veterans with PTSD and cognitive complaints. During recruitment, we will initially screen Veterans by phone. Those that are eligible for the study based on the phone screen will be brought to the lab for consenting, intake, and baseline assessments (approximately 200 Veterans). However, we assume a portion of those individuals will not qualify for the study. That will leave us with approximately 150 Veterans (75 per

condition) to randomize to treatment. For recruitment, we will utilize the VASDHS system of PTSD clinics, spanning the main and 3 satellite facilities, and general outpatient mental health clinics. The TBI Polytrauma Clinic and TBI Cognitive Rehabilitation Clinic will also be used as a source of recruitment since the majority of Veterans presenting to these clinics have comorbid PTSD. VA employees are not the target population, however they will not be excluded if they meet the inclusion criteria.

2. Inclusion/Exclusion Criteria:
Inclusion criteria are: 1) OEF/OIF Veterans enrolled at VASDHS, 2) aged 18-55 3) current PTSD diagnosis, 4) endorsement of cognitive complaints, 5) no pending medication changes, 6) English-speaking.

Exclusion criteria include: 1) active substance use disorder in the last month, 2) suicidal intent or attempt within the last month, 3) schizophrenia, psychotic disorder and/or bipolar disorder, 4) dementia, 5) premorbid IQ < 70, 6) participation in other concurrent PTSD intervention studies, 7) previous completion of more than 4 CPT sessions, 8) history of a documented neurological disorder (e.g., Parkinson's disease, multiple sclerosis, epilepsy) 9) moderate to severe TBI (loss of consciousness greater than 30 minutes or post-traumatic amnesia greater than 24 hours).

The exclusion criteria involving specific DSM-5 (Diagnostic and Statistical Manual-5) disorders, including substance use disorder, schizophrenia, psychotic disorder, bipolar disorder, and dementia (criteria 1, 3, 4) will be determined based on a CPRS chart review for clinical assessments that determine diagnosis based on DSM-5 criteria. We will also ask them during the phone screen about diagnoses. If there is any ambiguity in terms of psychiatric diagnoses based on the phone screen and a review of patient records (CPRS) that would disqualify the participant, the relevant portions of the MINI International Neuropsychiatric Interview (MINI; Sheehan, 2014) will be administered during the baseline assessment to clarify eligibility, as noted in the methods section. CPRS will also be reviewed for evidence of suicide intent or attempt within the last month (criteria 2), including a review of their Comprehensive Suicide Risk Assessment (CSRA) documented in CPRS. We will also ask them during the baseline assessment, including during the completion of the Beck Depression Inventory-II (BDI-II) that has a question about suicidal intent. An endorsement of a 1 or higher on this item will prompt further assessment for intent as described in the suicidality form. Premorbid IQ below our cutoff (criteria 5) will be determined either by a chart review if the participant received a previous clinical neuropsychological assessment documented in CPRS or by administering the WRAT5 during the baseline assessment (see methods section). Criteria 6, 7, 8, 9 will be determined by a CPRS chart review and also based on participant answers to the relevant questions on the phone screen. If the severity of any TBIs experienced (criteria 9) is ambiguous, eligibility will be determined by the Ohio State University TBI Interview administered at the baseline assessment (see methods section).

Veterans will not be excluded for current psychotropic medication usage or past mental health treatment that was not CPT ,but given the potential impact on outcome variables of interest, we will track duration and type of past mental health therapies as well as current medication use in enrolled Veterans.

Since the primary aim of the present research is centered around the intervention component, Veterans will still be enrolled in the study if they have contraindications for MRI, since that will not prevent them from engaging in and completing PTSD treatment in real-world settings; they will just not participate in the MRI portion of the study at baseline. In addition, the rate of exclusion for MRI-contraindications is very low. Contraindications for MRI include: pregnancy, cardiac pacemaker, metal fragments in eyes/body, participants who have been a metal worker /welder, aortic aneurysm clips, prosthesis, by-pass surgery/coronary artery clips, hearing aid, heart valve replacement, IUD, a shunt (ventricular or spinal), electrodes, metal plates/pins /screws/wires, or neuro/bio-stimulators (TENS unit), vision problems uncorrectable with lenses, claustrophobia, inability to lie still on one's back for approximately 60 minutes, prior neurosurgery, older tattoos with metal dyes, unwillingness to remove nose, ear or face jewelry, braces or permanent dental retainers.

No exclusions will be made based on gender, race or ethnic background. Gender and ethnic composition of the samples will reflect that of the population of eligible patients presenting from the recruitment sources.

Section 10.6 Avoiding coercion of students or employees

10.6) Indicate how coercion of students and/or employees will be avoided:

Although VA employees are not the target population, if they meet the inclusion criteria for the study they may be enrolled in this study. All study procedures with VA employees enrolled in this study will be done by staff who does not have a direct professional relationship or personal relationship with that employee.

Section 11 - Recruitment

11) Describe, step-by-step, the plans for recruitment of subjects (or selection of subjects as in record review). This description must include how, when, and where potential subjects are approached as well as procedures for identifying potential participants (through medical records, physician referral, third-party sources, etc.). Include how selection is equitable. Indicate if vulnerability to coercion may be present and if so plans to ensure voluntary participation.

The system of PTSD clinics within VA San Diego (spanning the main and 3 satellite facilities) and general outpatient mental health clinics will serve as primary recruitment clinics. The TBI Polytrauma Clinic and TBI Cognitive Rehabilitation Clinic will also be used as a source of recruitment since the majority of Veterans presenting to these clinics have comorbid PTSD. Research databases of Veterans who have previously consented to be contacted about additional study opportunities can also serve as a recruitment tool. We will provide informational, IRB stamped study brochures to Veteran Resource Centers and any psychological services centers at local higher education institutions. Additionally, we will use VA web, electronic board, and TV advertisements.

Additionally, to better target veterans who meet inclusion criteria for our study, research staff will search CPRS and pre-screen VASDHS patients who have previously received information about the current study from the Mission Valley or La Jolla VA PTSD Clinic Orientation Meeting for inclusionary criteria. Once patients who meet criteria are identified, research staff will send a recruitment letter via mail to these veterans prior to contacting them by phone. Those who are interested in participating will then undergo the standard phone screen and, if still determined eligible, will be scheduled for consenting.

We will also receive referrals from other VA studies. These studies will provide referrals of veterans have consented to be contacted for additional studies. Studies we will recruit from include protocol numbers
H150015, H130148, H150113, H130296, H170084, H180029, & H150106. Subjects from these studies who appear to be eligible for participation in this study and who have consented to be contacted about future research opportunities will be sent a recruitment letter via mail prior to contact by phone unless they have specifically consented to phone contact.

Additionally, we plan to contact veterans who have enrolled in the VA IRB approved registry, VASDHS TBI/PTSD Registry - H170023, allowing themselves to be contacted by future VA IRB studies. In section 12.10, we ask for a waiver of partial HIPAA so we can contact the Veteran via their preferred method of contact. If at any time, the Veteran enrolled in the VASDHS TBI/PTSD Registry lets this study know that they want to withdraw from the registry and no longer want to be contacted, we will contact H170023's study coordinator as soon as possible.

IRB-approved recruitment flyers will be posted in each targeted clinic with study telephone numbers listed and VA treatment providers will also share flyers and information about the study. Providers will request verbal consent from the Veteran to be contacted by study personnel if they report interest in participating in the study. Interested Veteran's can fill out our Research Interest Form or clinicians can refer via CPRS note to the PI, Dr. Crocker. Potentially eligible Veterans will be identified by study staff by phone contact from Veterans responding to flyers, interest form, or clinician referral. Study staff will provide detailed information about the study and its procedures via phone. For those Veterans who remain interested, they will undergo preliminary screening on the phone to determine that they meet basic inclusion criteria (e.g., demographics, diagnoses, cognitive complaints). If the phone screening suggests they meet basic criteria, they will be invited to undergo consenting and initial assessments that will confirm their study eligibility.

Only veterans who are currently receiving health care from the VASDHS will be enrolled. Study staff will provide detailed information about the study and its procedures to interested individuals. For those who agree to participate, study staff will arrange for consent and initial screening. Participants will take part in the study at the VA San Diego. All participants will be able to continue with any standard clinical care that they have been participating in or may be recommended by their doctor during the course of their participation in the study. Participants will enter the study on a consecutive admissions basis. We intend to recruit 200 Veterans in order to enroll 150 Veterans who qualify for study inclusion. Every reasonable effort will be made

to provide the informational brochure, "Volunteering in Research – Here Are Some Things You Need To Know" to potential research subjects.

Section 11.1 Recruitment Materials

11.1) Identify all recruitment materials (flyers, advertisements, letters, etc.) that will be used; include the web address for any web-based advertisements. The text of all communications with prospective participants must be reviewed and approved by the IRB before it can be used. You will be reminded to attach copies of recruitment materials to the initial submission packet. ***Note: Posting of flyers with pull tabs is not permitted within VASDHS (including the VMRF building). However, you may request to advertise on the e-boards (located at the elevators and throughout the facility) or on the VASDHS Research Opportunities web-page.***

We will be using an approved brochure and flyer that are provided to clinics at the VA in La Jolla, Mission Valley, Oceanside, and South County/Chula Vista and to Veterans Resource Centers and psychological services centers at local higher education institutions. We will also use an approved recruitment letter that will be sent to potential Veteran participants for those who previously agreed to be contacted for research purposes but did not explicitly agree to be contacted by phone. In addition to brochures, we use VA web, electronic boards, and advertisements posted on boards in the hospital and Veterans Medical Research Foundation.

Section 12 - Informed Consent

12) Indicate whether or not each category of consent is involved in this study:

12a) Will the study team obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without (or prior to) obtaining informed consent of the prospective subject or the prospective subject's LAR?

(•) Yes ( ) No

Check one or both of the below boxes if they apply to this study:

Information will be obtained through oral or written communication with the prospective subject or the subject's Legally Authorized Representative (LAR) and this is not a FDA regulated study.

(•) Yes ( ) No

Identifiable information or biospecimens will be obtained by accessing records or stored identifiable biospecimens and this is not an FDA regulated study.

(•) Yes ( ) No

If either or both of the above boxes is checked "yes", an informed consent waiver does not have to be requested for this activity if the protocol is initially approved after 01/01/2019 or if it has been converted to the 2018 Common Rule requirements. However, a request for a HIPAA waiver will still need to be requested and informed consent obtained for any research interventions after eligibility is established. Otherwise, waivers of consent and authorization must be requested for this activity. Waivers of consent and authorization are required for screening purposes for FDA regulated research.

12b) **Signed** informed consent

(•) Yes ( ) No

12c) Waiver of documented consent (e.g., **oral** consent) for all or part of the study.

( ) Yes (•) No

12d) Request for a **waiver** of consent for all or some study activities.

(•) Yes ( ) No

12e) Alteration of **other required elements** of consent.

( ) Yes (•) No

12f) **Child** assent to participate (Director approval will be required)

○ Yes ◉ No

12g) Will any language **other than English** be used by those obtaining consent and understood by the prospective participant or the legally authorized representative?

○ Yes ◉ No

12h) **Decisional Capacity Assessment** to determine if participants have the capacity to consent for themselves.

◉ Yes ○ No

12i) **Surrogate** consent (legally authorized representative)

○ Yes ◉ No

Section 12.1 Informed Consent Process

12.1a) Will consent be obtained before any study procedures are performed (including screening procedures except screening procedures with Consent and/or HIPAA waiver when required)?

◉ Yes ○ No

12.1b) Will the information being communicated to the participant or legally authorized representative during the consent process include exculpatory language through which the participant or legally authorized representative is made to waive or appear to waive any of the participant's legal rights or release or appear to release the Researcher, Sponsor, the VA or its agents from liability for negligence.

○ Yes ◉ No

12.1c) A master list of all VA subjects consented (written or not) under this protocol will be maintained.

◉ Agree ○ Disagree

12.1d) Identify the circumstances under which consent will be obtained including where the process will take place; any waiting period between describing the research and obtaining consent including sufficient time for the prospective participant to consider participation, and any steps taken to minimize the possibility of coercion or undue influence.

Participants will first hear details about the study during the phone screen process, at which time if eligible, they will be scheduled for consenting and an initial assessment. At the time of consenting (prior to the initial assessment), the study coordinator or the RA will explain the study to the participant and answer any questions the participant may have. After providing information about the study sufficient for the individual to make an informed decision about participating in the study, those who decide to participate will undergo the informed consent process by the study staff, who will be appropriately trained to obtain informed consent from the participants. Study staff will make sure the veteran has sufficient understanding of all aspects of the study, including time commitment, risks and benefits of participating, and the ability to withdraw from the study at any time with no impact on any clinical care they may receive or are receiving from the VASDHS, before obtaining written consent. Individuals will have as much time as is needed to make their decision about participating in the research. Furthermore, volunteers may discuss the study with a family member or other individual prior to consenting; informed consent will not be obtained until they have conferred with any and all individuals they feel necessary to make a fully informed decision to participate in research. All consent will be obtained in English; non-English speaking individuals will not be enrolled in this study. This consent process will be completed prior to undergoing any assessment or intervention/treatment related to the study. Informed consent will be obtained in person and within private office space within building 13. Participants will complete a decisional capacity quiz verifying that they understood the main components of the proposed research, their rights, and expectations during

the study. Though unlikely, if individuals cannot successfully complete this decisional capacity assessment and provide fully informed consent, they will not be enrolled in the current study. A Master List of all VA subjects consenting to this protocol will be maintained in a secured location.

Section 12.4 Waiver of Informed Consent

12.4a) Is it practicable to conduct the research without the waiver or alteration of consent?

○ Yes ◉ No

12.4b) Does the research examine public benefit or service programs and is subject to state or local government approval?

○ Yes ◉ No

12.4c) Will the research involve greater than minimal risk?

○ Yes ◉ No

12.4d) Will waiving or altering informed consent adversely affect the subjects' rights and welfare?

○ Yes ◉ No

12.4e) Is it appropriate to provide pertinent information to subjects later BUT this information will NOT be provided?

○ Yes ◉ No

12.4f) Identify to what aspects of the study you are requesting a waiver of consent (i.e., full study or specific aspects). Describe the waiver or alteration needed and why it can be granted (include why the research is not practical without the waiver or alteration and how the waiver enables conducting the study).

Waiver of informed consent or alteration of consent elements may be allowed if the IRB documents these findings and approves waiver or alteration.

Many research subjects are interested in other research and during the consenting process of the study, they participated in elect to be contacted for future research. These participants who previously participated in other research and have consented to be contacted for future research will be referred to us. In order to minimize inquiries to patients who do not qualify for this study by not meeting inclusion criteria or meeting exclusion criteria that is recorded in their CPRS file, a HIPAA waiver is needed for the study staff to be able to access the patient's CPRS file as a screening procedure to check eligibility for this study. This will allow us to not unnecessarily contact patients who clearly do not qualify to participate in this study. Information to be used to look up a patient in CPRS is the patient's name and the last four digits of the social security number.

Information to look at for eligibility includes diagnosis of PTSD, other mental health diagnoses including bipolar disorder, a psychotic disorder, or current substance use disorder, neurological disorder, history of participating in Cognitive Processing Therapy (CPT), history of moderate to severe traumatic brain injury, age, and OEF/OIF/OND status.

Additionally, a waiver is required for study staff to access VASDHS patient medical records in order to identify eligible patients who have received information about the current study from the Mission Valley or the La Jolla VA PTSD Clinic Orientation Meeting and to collect names, last four digits of the social security number, mental health information, addresses, and phone numbers for recruitment purposes. Patients identified as meeting criteria will be sent information about our study via mail prior to being contacted by study staff via phone.

Additionally, referrals from study H170023, the VA IRB approved VASDHS TBI/PTSD Registry, have given their documented oral consent to be contacted by future studies. We request a HIPAA waiver so we can contact the Veteran via his or her preferred method of contact.

Section 12.6 Decisional Capacity Assessment

12.6a) Describe the method(s) for determination of decisional capacity: (see ? for guidance) ***Please note that documentation of the assessement is required.***

The study staff who is informing the potential participant, after consenting will administer a short decisional capacity quiz to ensure sufficient decision making capacity of the participant. All answers should be answered correctly for the participant to pass the quiz. If a participant has a hard time with a questions, the study staff may give a more thorough explanation of the questions and give the participant another chance at answering the question.

12.6b) If subjects with limited decisional capacity will be enrolled, describe methods for obtaining subject assent or why they are not indicated:

Subjects with limited capacity will not be enrolled.

12.6c) If subjects with limited decisional capacity will be enrolled, describe procedures for respecting subject dissent and any additional safeguards or why these features are not needed:

Subjects with limited capacity will not be enrolled.

12.6d) If subjects with limited decisional capacity will be enrolled, describe the risk and, if greater than minimal, the relation to potential benefits:

Subjects with limited capacity will not be enrolled.

12.6e) If subjects with limited decisional capacity will be enrolled, describe the justification for the inclusion of any incompetent persons or persons with impaired decision-making capacity:

Subjects with limited capacity will not be enrolled.

Section 12.9 HIPAA Authorization

For each category below, indicate whether or not this study involves the indicated process:

12.9a) **Signed** HIPAA Authorization. ***New Template is available in the ? Help section***

(•) Yes ( ) No

12.9b) HIPAA waiver to cover the entire study

( ) Yes (•) No

12.9c) HIPAA waiver for recruitment, screening, and/or for a portion of the study.

(•) Yes ( ) No

12.9d) HIPAA Authorization or waiver is **not required** for some or all of the study subjects (e.g. no health data).

( ) Yes (•) No

Section 12.10 HIPAA Waivers and Alterations

12.10a) Describe the purpose/nature of the HIPAA waiver or alteration and list specifically, what identifiers and health information are being requested under the waiver/alteration and identify whether the waiver is for access, use, and/or collection of this information.

Many research subjects are interested in other research and during the consenting process of the study, they participated in elect to be contacted for future research. These participants who previously participated in other research and have consented to be contacted for future research will be referred to us. In order to minimize inquiries to patients who do not qualify for this study by not meeting inclusion criteria or meeting exclusion criteria that is recorded in their CPRS file, this HIPAA waiver is needed for the study staff to be able to access the patient's CPRS file as a screening procedure to check eligibility for this study. This will allow us to not unnecessarily contact patients who clearly do not qualify to participate in this study. Information to be used to look up a patient in CPRS is patient's name and the last four digits of the social security number.

Information to look at for eligibility includes diagnosis of PTSD, other mental health diagnoses including bipolar disorder, a psychotic disorder, or current substance use disorder, neurological disorder, history of participating in Cognitive Processing Therapy (CPT), history of moderate to severe traumatic brain injury, age, and OEF/OIF/OND status.

Additionally, a waiver is required for study staff to access VASDHS patient medical records in order to identify eligible patients who have received information about the current study from the Mission Valley or the La Jolla VA PTSD Clinic Orientation Meeting and to collect names, last four digits of the social security number, mental health information, addresses, and phone numbers for recruitment purposes. Patients identified as meeting criteria will be sent information about our study via mail prior to being contacted by study staff via phone.

Additionally, referrals from study H170023, the VA IRB approved VASDHS TBI/PTSD Registry, have given their documented oral consent to be contacted by future studies. We request a HIPAA waiver so we can contact the Veteran via his or her preferred method of contact.

12.10b) The proposed access, use, and/or disclosure of PHI involves no more than a minimal risk to the privacy of individuals.

(•) Agree ( ) Disagree

12.10c) The plan to protect the identifiers from improper use and disclosure is adequate.

(•) Agree ( ) Disagree

Describe the plan

The identifiers will not be released to any other research study and the only hard copy will remain in a locked file cabinet in VMRF Building 13, room 312H. Only this study staff has access to the identifiers.

12.10d) An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.

(•) Agree ( ) Disagree

12.10d2) Describe the plan:

Data will only be destroyed according to RCS-10 under Records Control Manager guidance.

12.10e) By signing this protocol for submission, the PI is providing written assurance that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by the Privacy Rule. 38 U.S.C. 7332 Information: If the waiver of HIPAA authorization is for the use of 38 USC 7332 information (applicable to drug abuse, alcohol abuse, HIV infection, and sickle cell anemia records), by signing this protocol for submission the PI is providing written assurance that the purpose of the data is to conduct scientific research and that no personnel involved 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. (Ref: 38 U.S.C. 7332(b)(2)(B))

(•) Agree ( ) Disagree

12.10f) The research could not practicably be conducted without the waiver or alteration.

(•) Agree ( ) Disagree

12.10f2) Describe how the waiver/alteration enables the research to be conducted

The waiver will enable us to screen the patients who previously consented to be contacted for other research by accessing their CPRS file to check their eligibility for participation in this study by confirming diagnoses and therapy history. Then, a phone call will be made to those who meet the eligibility criteria. The waiver will also enable us to conduct a phone screen to prevent scheduling veterans who are ineligible to participate.

12.10g) The research could not practicably be conducted without access to and use of the PHI.

(•) Agree ( ) Disagree

12.10g2) Describe why it would be impracticable to conduct this research without the PHI described 12.10a. (v3 /8/18)

Once we obtain a waiver, the study staff will be able to use patient's name and last four digits of the social security number to access the patient's CPRS record. Study staff will then screen patients with inclusion/exclusion criteria information in their CPRS file before making a phone call.

Section 13 - Alternatives to Participation

13) Describe the alternatives to participation in this research study (see ? for guidance)

If an individual chooses to not participate or withdraw from participation in this study, they will be offered the option to be referred to standard clinical CPT or other mental health treatment done with no research component. There may be risks associated with standard treatments for PTSD that they can review with their health care provider.

Section 14 - Potential Risks

14) Describe any potential or known risks or discomforts and assess their likelihood and seriousness (see ? for guidance)

The first safety issue for this study is related to MRI scanning. MRI is a noninvasive procedure and overall, risks for MRI scanning are minimal given appropriate screening, which is done via an initial phone interview and again immediately prior to scanning. There are no known adverse effects from exposure to magnetic fields. To ensure the safety and comfort of all subjects, we will exclude those with a history of claustrophobia, difficulty lying flat for long periods, or anyone with any metal or a pacemaker in the body. Potential risks include discomfort while lying still in a confined space during imaging; claustrophobia; and fatigue from the approximately 1 hour of total time for the MRI scan procedure. In addition, there are risks of bodily harm associated with MRI imaging if the subject has metal in his or her body, or wears a pacemaker.

There is the possibility of an abnormal finding on the MRI scan. However, the MRI scans are not being done for clinical purposes, and the MRI scan procedure is not sufficient for the clinical diagnosis of a possible brain disorder. The purpose of this scan is not to diagnose abnormalities, but on rare occasions a finding is observed that might be clinically important. Should there be cause for concern, with permission of the participant, this information will be forwarded to his /her primary care physician for follow-up.

Another risk of participating in the study include emotional discomfort as participants are being asked to discuss difficult personal topics. Participation in this study may involve some added risks or discomforts associated with anxiety and reactions to trauma which can lead to temporary

increases in discomfort. Emotional discomfort and associated anxiety typically subside as the skills taught in treatment are learned. Participants can decline to answer questions that make them uncomfortable. Study staff are also trained to handle any distress that arises and participants will be provided with information on who to contact during and after standard business hours in the event of any distress or concern. Study staff or emergency/crisis personnel will be available 24 hours a day to offer additional intervention, treatment, or make emergency referrals if necessary. If participants choose to withdraw early from the study or study staff feels it is in a patient's best interest, they will be offered the option to enter standard clinical treatment with no research component. Should any participant present a danger to self or others related to suicidal intent, homicidality, or other acute psychiatric issue, standard clinical interventions to ensure safety and stabilization will be implemented and the participant will be withdrawn from the study if necessary.

Another risk of participation in this study is fatigue and/or boredom during the assessments. Frequent rest intervals will be available during the testing periods to reduce fatigue.

All data will be collected specifically for research purposes and treated in a confidential manner. Loss of confidentiality is a risk of participating in research; as a result of participation in this project, there is a very small risk that sensitive information (e.g., diagnostic information) could become known outside the research setting. Significant efforts relating to data security keep this risk exceptionally low.

Finally, since this is an investigational study, it may involve risks that are currently unforeseeable. This is explained to the participant and if new risks become known in the future, participants will be informed of them. Similarly, participants will be told if any important new information is found during the course of this study that may affect wanting to continue as a participant.

Section 15 - Risk Management

15) Describe the procedures for protecting against or minimizing any potential risks/discomforts, and the adequacy of resources for conducting the study and resources participants may need as a consequence of the research. When applicable, include detail of the following safety measures: (a) The type of safety information to be collected, including AEs; (b) Frequency of safety data collection; (c) Frequency or periodicity of review of cumulative safety data; (d) Statistical tests for analyzing the safety data to determine if harm is occurring; and (e) Conditions that trigger an immediate suspension of the research. See ? for further requirements.

MRI: Overall, risks for MRI scanning are minimal given appropriate screening, which is done via an initial phone interview and again immediately prior to scanning. We will use a standard MRI screening form currently in use by the Keck Center for fMRI, which frequently performs research MRI studies. This instrument has been used successfully in past protocols to exclude patients with suspected or known risk factors. If the screening form elicits any suspected risk factors, the form will be supplemented by review of medical records with the subject's permission. Finally, subjects will be asked the screening questions one more time by the MRI technician before being placed in the magnet and will be apprised of the risks as part of signing the consent form.

Exposure to a high magnetic field. Subjects will be screened for implanted materials and devices during the initial screening assessment. Moreover, all subjects will be re-screened before they will be allowed to enter the MRI facilities. Any non-removable magnetic or electrical material will automatically exclude subjects. A trained MR technician will scan the participants. The MR scanner at the UCSD Center for Functional MRI has a field strength of 3.0 Tesla. Imaging at this field strength is not considered a significant risk according to FDA guidelines. Because the pulse sequences to be used are commonly used research sequences, we do not expect any hazard associated with power deposition.

Peripheral nerve stimulation from rapidly switched magnetic fields. Participants will be informed about the possibility of stimulation effects during the informed consent process. We will monitor the subject's status during the scan about their comfort level and unexpected sensorimotor experiences. If a subject reports stimulation effects, we will remove the subject from the scanner and terminate the subject's participation in the study.

Claustrophobia. Usually this is manifested in the first couple of minutes after the person is placed in the magnet. We inquire about comfort and if the subject complains of discomfort or anxiety, we will immediately remove them from the magnet. Often our prompt response allays their concern and they chose to continue. If the participant decides they are too uncomfortable to continue, we end their participation in the fMRI scan.

Physical discomfort and fatigue. These risks usually develop slowly over the course of the scans. Discomfort can be minimized by careful placement of neck, head, and leg supports when a participant is placed in the magnet. Fatigue can be reduced by appropriate pacing of the study scans. The scan operator will ask about a participant‘s comfort every 5 to 10 minutes. If a subject becomes too uncomfortable to continue, she/he will be removed from the scanner but removed from the study only if they request to end their participation.

Acoustic noise. Subjects will be instructed to wear earplugs or headsets that reduce the noise by about 20-40 dB. They will also be instructed to indicate if the noise is a source of physical or psychological discomfort. If discomfort occurs the fMRI scan will be terminated.

Pregnancy. At this time it is unknown whether or not there are potential risks to a fetus from exposure to magnetic fields (MRI). For studies that involve MRI, fMRI, and similar scans, women of childbearing potential must be excluded from this part of the study if a pregnancy test is positive or if the subject thinks that she might be pregnant.

Other potential MR risks. The subject will be informed during the consent process that the scans are not optimal for diagnosing a brain disorder. Yet some abnormalities might be observed on the scans. Should there be cause for concern, with permission of the participant, any clinically important observations will be forwarded to his/her primary care physician for follow-up. Although it is possible to reconstruct a form of the facial features from the MRI data, the likelihood that this information could be used to identify a person with the reliability of a photograph has not been confirmed by research to date, making these reconstructions not comparable to photographic images. It is preferable to maintain the facial features in the MR images for purposes of later data analysis and skull reconstruction. As part of the authorization and informed consent process, subjects will be informed of the slight risk of potential identification based on reconstruction of MR images and will give authorization to disclose this information to study investigators.

The process of being asked about the presence of a mental health diagnosis during the telephone screen may cause temporary discomfort and Veterans can be reminded of immediately accessible clinical services available to them (e.g., VA Psychiatric Emergency Clinic) in the event of any significant discomfort.

Risk of emotional discomfort that can arise during Cognitive Processing Therapy will be addressed in that all Veterans will see their study therapist biweekly to weekly for the therapy component of the study. Dr. Crocker will review the assessment and progress of each subject and consult with Dr. Jak during weekly meetings. The clinical experience and skill level of personnel will enable study staff to implement protocol procedures with a minimum of psychological discomfort for study participants. All patients will be monitored on a weekly basis, and study personnel will be available during regular business hours to respond to patients’ concerns and participants will have emergency contact information for after-hours concerns.

There is always a risk associated with the management of patients with mood and anxiety disorders that they will develop suicidality. This risk will be carefully mitigated by the systematic and careful assessment of suicidality and homicidality throughout the protocol via weekly in-session assessments made by the therapists. Subjects who develop suicidality will be evaluated by therapist, Dr. Crocker, and Dr. Jak to determine whether continued participation in the study is safe and clinically warranted. If the study personnel and participant feel that discontinuation would best suit the participant, the participant will be discontinued from the study, and the participant will be reviewed for appropriate treatment. All mental health staff are trained in and required by the VA to regularly assess suicidality and/or homicidally. If a patient endorses suicidal ideation or homicidal ideation, standard safety procedures are implemented via a licensed psychologist. These depend on the level of threat presented by the patient and may range from making a safety plan with the patient to implementing 5150 procedure for an inpatient hold. Homicidal ideation additionally involves assessment of whether to invoke the Tarasoff law.

For participants who wish to terminate prematurely, we will request a final meeting to assess clinical status and safety and to review reasons for withdrawal (if the participant is willing to share them). Referrals for alternative mental health services, including those in our clinics outside this protocol, will also be provided. Participants enrolled in the study may withdraw at any time without penalty or loss of any benefits or treatment options available to them. Investigators may also withdraw a participant from the study for treatment non-compliance or a newly developed psychiatric or medical problem if, in the opinion of the investigators, these factors interfere with the participant’s ability to participate fully in the study. If a participant discontinues the study for any reason, he/she will be offered and allowed access to any care in our clinics that any other patient not associated with the study would receive.

The risk of fatigue and boredom possibly related to neuropsychological testing will be mitigated by examiners making the tests as interesting to the participants as possible and offering numerous breaks over the course of the assessment period. Veterans do not need to answer any question or complete any test that makes them uncomfortable. To minimize undue influence and risks, research participants/VA employees that are directly supervised by the PI will be consented by a different member of the research team, and any research personnel that may have a personal affiliation with the research participants/VA employee will not be involved in consenting nor perform the research procedures; and where applicable, any research personnel that may have a personal affiliation with the research participant/VA employee will not have access to code keys of the coded data, medical records/CPRS notes, and employee records.

The subjects' confidentiality will be strictly maintained. Consent and other forms containing identifying data will be kept separate from other research data. All personal identifying information that includes diagnosis and/or medical status will be kept in a locked cabinet where access can be strictly controlled. Other research records will be numerically coded to remove any identifying information. Computer and other data records will be coded so the subjects' identity cannot be directly ascertained. All computerized cognitive testing data will also be de-identified and coded with only an ID number and thus will contain no Protected Health Information (PHI). One key document connecting the names with the codes will be maintained and kept by the researcher. All data will be kept locked in the offices of the researcher or other appropriately trained research staff. Research records will be kept completely confidential to the extent provided by law, and the participant's identity will not be disclosed without their written consent unless required by law. Only the study staff in this project will have access to these records.

COVID-19 Modification Safety Measures: While COVID-19 remains a public health risk all face-to-face appointments will be minimized to ensure safety. The majority of assessment measures originally completed during in-person visits and all therapy sessions will be completed via teleconference and phone. For all practical purposes, the provision of mental health services by telemedicine is considered routine clinical care within the VHA. We will follow the Standard Operating Procedures Manual developed by Peter Shore for Home-Bases Telemental Health in VISN 20. All COVID-19 guidelines established by the VA San Diego Healthcare System and Research Service will be closely followed to ensure participant safety during the abbreviated in-person visits.

Section 17 - Potential Benefits

17) Discuss benefits that may be gained by the subject as well as potential benefits to society in general (see ? for guidance)

Participants may or may not experience benefits from participation in this study. Participants may experience reduction in symptoms related to PTSD over the course of the study, including reduction of emotional distress and improvement in quality of life and cognitive abilities. In addition, the knowledge derived from this study may be of considerable benefit in terms of improving treatment for PTSD for future Veterans.

Section 18 - Risk/Benefit Analysis

18) Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may reasonably be expected to result.

The risks involved with neuroimaging, clinical assessment, cognitive training, and psychotherapy appear justified by the potential benefits to the subject of the provision of treatment by a skilled therapist, potential improvements in PTSD cognitive and emotional symptoms and thus quality of life. There is also potential gain from finding ways to improve treatment for all Veterans with PTSD. As compared to these potential benefits, the risks to subjects appear reasonable and justified.

Section 20 - Compensation for Participation

20) Provide all details and justifications of the compensation plan. See ? for detailed requirements.

Participants will be compensated for their time after each completed assessment. Veterans will receive $50 for the baseline assessment ($30 for completion of the questionnaires and

neuropsychological assessment, $20 for the fMRI assessment), $30 as a bonus for completing at least 80% of the cognitive training (or placebo word games), $50 for the post-computerized training assessment, and $70 for the post-therapy assessment (Total possible = $200). If participants attend a given assessment, they will be paid the entire amount per assessment regardless of whether they complete the entire assessment.

Section 21 - Responsibilities and Qualifications

Here are the identified study staff members

Laura D. Crocker, PhD

Amy J. Jak, PhD, Jessica A. Bomyea, PhD, Peter J. Colvonen, PhD, Sonya B. Norman, PhD, Victoria C. Merritt, PhD, Alexandra O. Higdon, PsyD, Amber Victoria Keller, Samantha N. Hoffman, Delaney K. Davey, Shahrokh Golshan, PhD, Cody Witten, Jackson Schierbeek, Jillian Leigh Ory, BA, Morgan E. Marvin, BA, Sarah Jurick Lefler, PhD

21) For each staff member listed above, describe their role and qualifications. Also indicate which of the study staff are authorized to obtain consent, when applicable to the study.

Dr. Crocker (PI) and Dr. Jak (Co-PI) will oversee the overall direction of the project, including the development, coordination, implementation, and monitoring of program activities. Drs. Crocker and Jak will carry the major responsibility for supervising all aspects of project activities. Specifically, they will be responsible for general study oversight, supervision and assurance of regulatory approvals, and training and supervision of staff related to subject recruitment, phone screening, consenting, CPT, MRI data collection, and neuropsychological assessments. They will also coordinate data analysis and manuscript preparation. Dr. Crocker will be the study therapist and will deliver therapy to participants, as well as enter visit notes in CPRS.

Both PIs will be authorized to obtain consent and test participants will guide the protocol through the IRB, VA research and development committee, HRPO, and other regulatory approval processes, recruit and consent volunteers, maintain study records, enter data into a computer database.

Samantha Hoffman (Research Associate): Authorized to assist with recruitment and screening of participants, obtain informed consent, test participants, collect MRI data, administer and score assessments, perform data entry, maintain study records. She will work closely with and assist PIs.

Amber Keller (Research Associate): Authorized to assist with recruitment and screening of participants, obtain informed consent, test participants, collect MRI data, administer and score assessments, perform data entry, maintain study records. She will work closely with and assist PIs.

Sonya Norman, Ph.D. (Co-PI): Will be responsible for the oversight and supervision of study staff related to data collection and clinical intervention, as well as CPRS clinical notes. She will work closely with PIs.

Peter Colvonen, Ph.D. (Co-PI): Will be responsible for the oversight and supervision of study staff related to data collection and clinical intervention, as well as CPRS clinical notes. He will work closely with PIs.

Shahrokh Golshan, Ph.D. (Biostatistician): Will be responsible for participant study randomization and statistical analyses.

Sarah Jurick Lefler, Ph.D. (Post-Doc): Authorized to obtain consent and test participants, maintain study records, enter data into a computer database. This person will work closely with project participants, investigators, and staff. Also will administer and score assessments as described in section 9 and will conduct image acquisition and post-processing. She will work closely with the PI and will also assist with data analysis and manuscript preparation.

Cody Witten (Student Volunteer): Authorized to obtain consent and test participants, recruit and consent volunteers, maintain study records, enter data into a computer database. This person will work closely with project participants, investigators, and staff. Also will administer and score assessments as described in section 9 and will conduct image acquisition and post-processing. He will work closely with the PI and will also assist with data analysis and manuscript preparation.

Delaney Davey (Study Coordinator): Authorized to guide the protocol
through the IRB, VA research and development committee, HRPO, and other regulatory approval processes recruit and screen participants, obtain informed consent, test participants, collect MRI data and post-processing, administer and score assessments, perform data entry, maintain study records, as well as enter visit notes into CPRS. She will work closely with and assist PIs.

Alexandra Higdon, Psy.D. (Research Psychologist): Authorized to assist with recruitment and screening of participants, obtain informed consent, test participants, administer and score assessments, perform data entry, maintain study records. She will work closely with and assist PIs. Dr. Higdon will be a study therapist and will deliver therapy to participants, as well as enter visit notes in CPRS.

Victoria Merritt, Ph.D. (Co-PI): Will be responsible for the oversight and supervision of study staff related to data collection and clinical assessments. She will work closely with PIs.

Jillian Ory (Research Associate): Authorized to assist with recruitment and screening of participants, obtain informed consent, test participants, collect MRI data, administer and score assessments, perform data entry, maintain study records. She will work closely with and assist PIs.

Jackson Schierbeek (Research Associate): Authorized to assist with recruitment and screening of participants, obtain informed consent, test participants, collect MRI data, administer and score assessments, perform data entry, maintain study records. He will work closely with and assist PIs.

Jessica Bomyea, Ph.D. (Co-PI): Authorized to obtain consent and test participants, maintain study records, enter data into a computer database. She will work with project participants and will oversee and supervise staff related to data collection and assessments. Also will conduct image post-processing and data analysis. She will work closely with the PIs and will assist with manuscript preparation.

Morgan Marvin (Research Associate): Authorized to assist with recruitment and screening of participants, obtain informed consent, test participants, collect MRI data, administer and score assessments, perform data entry, maintain study records. She will work closely with and assist PIs.

Section 22 - Bibliography

22) List relevant articles that the IRB can use to provide necessary background for the protocol. Do not include an extensive NIH-grant-style bibliography. (Up to 5 recommended, but use more if needed to support the protocol or citations above.)

1. Aupperle, R. L., Melrose, A. J., Stein, M. B., & Paulus, M. P. (2012). Executive function and PTSD: Disengaging from trauma. Neuropharmacology, 62(2), 686–694.
2. Badura-Brack, A. S., Naim, R., Ryan, T. J., Levy, O., Abend, R., Khanna, M. M., … Bar-Haim, Y. (2015). Effect of attention training on attention bias variability and PTSD symptoms: Randomized controlled trials in Israeli and U.S. Combat Veterans. American Journal of Psychiatry, 172(12), 1233–1241.
3. Bradley, R., Greene, J., Russ, E., Dutra, L., & Westen, D. (2005). A multidimensional meta-analysis of psychotherapy for PTSD. American Journal of Psychiatry. 162, 214–227.
4. Chard, K. M., Schumm, J. A., Owens, G. P., & Cottingham, S. M. (2010). A comparison of OEF and OIF veterans and Vietnam veterans receiving cognitive processing therapy. Journal of Traumatic Stress, 23(1), 25–32.
5. Crocker, L. D., Heller, W., Warren, S. L., O'Hare, A. J., Infantolino, Z. P., & Miller, G. a. (2013). Relationships among cognition, emotion, and motivation: implications for intervention and neuroplasticity in psychopathology. Frontiers in Human Neuroscience, 7, 261.
6. Erbes, C. R., Curry, K. T., & Leskela, J. (2009). Treatment presentation and adherence of Iraq /Afghanistan era veterans in outpatient care for posttraumatic stress disorder. Psychological Services, 6(3), 175–183.
7. Falconer, E., Allen, A., Felmingham, K. L., Williams, L. M., & Bryant, R. A. (2013). Inhibitory neural activity predicts response to cognitive-behavioral therapy for posttraumatic stress disorder. The Journal of Clinical Psychiatry, 74(9), 895–901.
8. Garfinkel, S. N., & Liberzon, I. (2009). Neurobiology of PTSD: A review of neuroimaging findings. Psychiatric Annals, 39(6), 370–381.
9. Hayes, J. P., Hayes, S. M., & Mikedis, A. M. (2012). Quantitative meta-analysis of neural activity in posttraumatic stress disorder. Biology of Mood & Anxiety Disorders, 2(1), 9.

10. Kehle-Forbes, S. M., Meis, L. A., Spoont, M., & Polusny, M. A. (2015). Treatment initiation and dropout from prolonged exposure and cognitive processing therapy in a VA outpatient clinic. Psychological Trauma: Theory, Research, Practice, and Policy, 8, 107–114.
11. Keshavan, M. S., Vinogradov, S., Rumsey, J., Sherrill, J., & Wagner, A. (2014). Cognitive training in mental disorders: Update and future directions. American Journal of Psychiatry, 171, 510-522.
12. Klingberg, T. (2010). Training and plasticity of working memory. Trends in Cognitive Sciences, 14(7), 317-324.
13. Kuckertz, J. M., Amir, N., Boffa, J. W., Warren, C. K., Rindt, S. E. M., Norman, S., … McLay, R. (2014). The effectiveness of an attention bias modification program as an adjunctive treatment for post-traumatic stress disorder. Behaviour Research and Therapy, 63, 25-35.
14. Li, H., Li, J., Li, N., Li, B., Wang, P., & Zhou, T. (2011). Cognitive intervention for persons with mild cognitive impairment: A meta-analysis. Ageing Research Reviews, 10, 285-296.
15. Merzenich, M. M., Van Vleet, T. M., & Nahum, M. (2014). Brain plasticity-based therapeutics. Frontiers in Human Neuroscience, 8, 385.
16. Mohlman, J., & Gorman, J. M. (2005). The role of executive functioning in CBT: A pilot study with anxious older adults. Behaviour Research and Therapy, 43(4), 447–465.
17. Monson, C. M., Schnurr, P. P., Resick, P. A., Friedman, M. J., Young-Xu, Y., & Stevens, S. P. (2006). Cognitive processing therapy for veterans with military-related posttraumatic stress disorder. Journal of Consulting and Clinical Psychology, 74, 898-907.
18. Morey, R., Petty, C., & Cooper, D. (2008). Neural systems for executive and emotional processing are modulated by symptoms of posttraumatic stress disorder in Iraq War veterans. Psychiatry Research, 162, 59-72.
19. Mott, J. M., Mondragon, S., Hundt, N. E., Beason-Smith, M., Grady, R. H., & Teng, E. J. (2014). Characteristics of U.S. Veterans who begin and complete prolonged exposure and cognitive processing therapy for PTSD. Journal of Traumatic Stress, 27(3), 265–273.
20. Patel, R., Spreng, R. N., Shin, L. M., & Girard, T. a. (2012). Neurocircuitry models of posttraumatic stress disorder and beyond: A meta-analysis of functional neuroimaging studies. Neuroscience & Biobehavioral Reviews, 36(9), 2130–2142.
21. Polak, A. R., Witteveen, A. B., Reitsma, J. B., & Olff, M. (2012). The role of executive function in posttraumatic stress disorder: A systematic review. Journal of Affective Disorders, 141 (1), 11–21.
22. Riemann, B. C., Kuckertz, J. M., Rozenman, M., Weersing, V. R., & Amir, N. (2013). Augmentation of youth cognitive behavioral and pharmacological interventions with attention modification: A preliminary investigation. Depression and Anxiety, 30(9), 822–828.
23. Schottenbauer, M. a, Glass, C. R., Arnkoff, D. B., Tendick, V., & Gray, S. H. (2008). Nonresponse and dropout rates in outcome studies on PTSD: Review and methodological considerations. Psychiatry, 71(2), 134–168.
24. Vinogradov, S., Fisher, M., & de Villers-Sidani, E. (2012). Cognitive training for impaired neural systems in neuropsychiatric illness. Neuropsychopharmacology, 37(1), 43–76.

Section 27 - Privacy, Confidentiality, and Information Security

27a) Provide a brief description of how participant privacy and confidentiality will be protected in this study. Describe the circumstance under which it may be possible for a research team member to identify subjects and any related protections or assurances to prohibit or avoid identification. Describe how the number of people with access to identifiers for research purposes is limited in order to protect a participant's privacy.

Research records will be kept confidential to the extent provided by law. All personal identifying information that includes diagnosis and/or medical status will be kept on the VA's secure computer system or in a locked cabinet where access can be strictly controlled. Research records will be numerically coded with a unique identifier to remove any personally identifying information. Because
names must appear on the consent form, it will be stored in a file separate from the other hard copy data. All hard copies of data collection sheets will be kept in locked file cabinets inside of locked offices in the VA belonging to the research staff (Bldg 13, room 306H or 312H). The participant name-to-code
conversion sheet will be stored in a locked file cabinet, inside of a locked office, accessible only to the researchers and to those project staff with a need for this information. The participant name-to-code conversion sheet will be secured separately from the research data. Participants will not be identified in
any reports or publications. Access to these records will be limited to the researchers and project staff who have a need to access the information to carry out the research. Appropriate parties other than the research staff may be granted access to the study data as required (e.g., VASDHS Research and Development Personnel; VA IRB personnel; and/or medical monitors); these

individuals will be bound by
the same rules of confidentiality as the investigative team. Data will be destroyed according to RCS10 guidelines after the completion of the study and will be destroyed by approved methods at that time.
Social security numbers will be collected for access to the Veteran's CPRS medical record as well for payment to the Veteran for participation in the study. These social security numbers will be stored securely on the VA's secure computer system or for hard copy payment records, they will be stored in a locked file cabinet in a locked office in Building 13, room 306H or 312H. Refer to the VA Privacy and Data
Security Plan for further detail.

27.b) Entry of a CPRS Research Informed Consent Note is required when subjects will be admitted as inpatients or treated as an outpatients for research *and* the study involves research medical care or may affect medical care.

- ***If a Research consent Note is required, then a Research Progress Note should also be entered for each procedure or intervention.***
- ***Scanning the Consent and HIPAA Authorization into CPRS is not required. Linking the Consent to the Research Informed Consent Note may be permitted and can be useful for trials involving the Research Pharmacy or when research will be performed in conjunction with clinical procedures.***
- ***For Non-Veterans, if Research Informed Consent Notes are entered, then the NOPP Acknowledgment must be scanned into the record. Otherwise a copy of the signed NOPP must be retained with the Investigator's research records and a copy sent to the Privacy Officer; see the ? Help for more information.***

27.b1) Is entry of CPRS notes required based on the above criteria?

- (•) CPRS notes are needed for ALL subjects
- ( ) CPRS notes are needed for SOME subjects
- ( ) CPRS notes are NOT needed for any subjects

27c) Select the VA Sensitive Information (VASI) use category

- ( ) This study does not collect or use any VASI
- ( ) This study uses but does not save, collect, copy, or record VASI
- (•) This study does collect or record VASI

Section 27.1 VA Sensitive Information (VASI)

27.1a) For each type of VASI, indicate all that apply:

Indicate which of the following will be collected/recorded:

- [x] Protected Health Information (PHI)
- [x] Names
- [ ] Device identifiers and serial numbers
- [ ] E-mail addresses
- [ ] Medical record numbers
- [ ] URLs (Universal Resource Locator)
- [ ] All elements of dates (except year) or any age over 89
- [ ] Health plan beneficiary numbers
- [ ] IP Addresses (Internet Protocol)
- [x] Telephone numbers
- [x] Account numbers
- [ ] Biometric Identifiers including finger and voice print
- [ ] Fax numbers

- [ ] Certificate or license numbers
- [x] Full face photographic images and comparable images
- [ ] All geographic subdivisions smaller than a state
- [ ] Vehicle ID and serial numbers including license plate numbers
- [x] Social security numbers or scrambled SSNs (describe below)
- [ ] Other unique identifying number, characteristic, or code (describe below)

27.1a1) Describe why SSN are needed for this study

Social security numbers will be collected for access to the Veteran's CPRS medical record as well for payment to the Veteran for participation in the study.

27.1b) Consent Forms and/or HIPAA Authorization

(•) Yes ( ) No

27.1c) Images with personal identifiers are used for this study (x-rays, MRI images with patient names, record numbers, dates, etc.)?

( ) Yes (•) No

27.1d) Photos with faces or audio video recordings are used for this study.

( ) Yes (•) No

27.1e) Biological specimens with identifiers are used for this study.

( ) Yes (•) No

Section 27.2 Data Collection, Tools, and Resources

27.2a) Will any specially obtained software be used?

( ) Yes (•) No

27.2b) Will any mobile devices (laptop, tablet, portable hard-drive, etc.) be used in support of this study?

(•) Yes ( ) No

27.2b1) Provide details of the device/s. Indicate whether the device is FIPS 140-2 encryption validated and confirm that the device is listed in the VA EIL. Provide details regarding the nature of the data that will be stored or transmitted on the device and confirm whether a copy of all data will be stored on the VA network.

VMRF laptop computer will be used to collect non-VASI behavioral data (664 EE111331). A copy of all behavioral data will be transported to the R drive using VA-issued encrypted thumb drive

and stored permanently on R:\Crocker.

If study staff are sent home to telework as part of the COVID-19 emergency response then staff will deliver psychotherapy and assessments using secure video conferencing on either a VA laptop or personal laptop via VA remote access. No data from the secure video conference will be stored on personal devices.

27.2c) Does the study require use of an electronic data capture system?

○ Yes ◉ No

27.2d) Will any other web-based applications be used (e.g., for recruitment, completing online questionnaires, or processing data)?

◉ Yes ○ No

27.2d1) Provide the web address, details regarding their security features, the nature of the data involved, and the research purpose. Also include a description of how VA retains a copy of the data generated using these tools.

Regarding the cognitive training that will be administered via BrainHQ (https://research.brainhq.com), data transport and storage systems are HIPAA and FIPS-140 compliant. No personally identifiable information is mandatory to use the BrainHQ program. User names will be coded as anonymized, de-identified study numbers or
otherwise de-identified. The only information created, transmitted, and stored by the program pertains to usage (e.g., how much training has been done) and progress (e.g., how much improvement has been calculated) that a user makes. IP addresses are not recorded to be in HIPAA compliance. Also, data will be downloaded from BrainHQ on a regular basis and stored on the secure VA network drive.

REDCap is a free, secure Web application (only accessible on a VA computer) that facilitates the collection and entry of research data. This study will use REDCap for entry of research data only (not for completing online questionnaires). Only authorized study staff will be able to access the REDCap database. This tool helps VA researchers enter, store, and manage their project data in a systematic manner. Guidance on accessing and using VA REDCap is available to researchers with VA network access by copying and pasting the following URL into the browser: http://vaww.virec.research.va.gov/REDCap/Overview.htm.

Data from REDCap will be occasionally exported to an excel or SPSS file and stored on the R-drive behind the VA firewall.

27.2e) Will coded data that excludes personal identifiers be used? Coded data excludes *all* HIPAA identifiers (per VHA Handbook 1605.1 Appendix B), including dates

◉ Yes ○ No

27.2e1) Identify where the code key is stored and in what format (electronic, paper).

A key code that links participants with their coded identifier will be maintained by Dr. Crocker. This key code will be stored in hard copy format in locked file cabinets in locked rooms in VASDHS Building 13 and will be stored separately from all other study data and available only to Dr. Crocker and her research coordinator. The key code will also be stored electronically in a password-protected file in a limited access folder on the secure VA network drive.

Section 27.3 Data Sharing and Transportation

27.3a) Does this study involve collecting, sharing or transporting any type of data outside of the local VA?

○ Yes ◉ No

Section 27.4 Research Record Storage and Retention

For each type of record, indicate whether it is collected for this study

27.4a) Hardcopy records/data (includes paper, pictures, film, etc.)

◉ Yes ○ No

27.4a1) Identify precisely where hardcopy data will be stored to include physical site, building, and room number, etc. For each location identify whether VASI or non-sensitive information is stored at that location. For VASI, identify how the data is secured.

All hard copies of VASI information will be kept in locked file cabinets inside of locked offices in the VA belonging to the research staff (Bldg 13, room 312H). VASI information will be accessible only to the researchers and to those project staff with a need for this information. The participant name-to-code
conversion sheet will be secured separately from the research data.

All non-sensitive information hard copies of data collection sheets will be kept in locked file cabinets inside of locked offices in the VA belonging to the research staff (Bldg 13, room 306H or 312H).

27.4a2) Are all of the above locations at VA?

◉ Yes ○ No

27.4b) Electronic study records (includes computer files, removable disk files, digital files, etc.).

◉ Yes ○ No

27.4b1) Identify precisely where ***non-sensitive*** electronic records/data will be stored to include the full map drive, network location/server name, etc., and a brief description of what data/information is stored at each location.

Electronic non-sensitive files will be stored in the Jak drive on the SAN network on the VMRF server designated for Dr. Jak (Jak server).

De-identified data will be stored through the VA REDCap system, which is only accessible on a VA computer network with a VA login. Non-sensitive data will also be encrypted and stored on the R drive (R01SDCHSM02.R01.Med.Va.gov\Crocker). Only essential study personnel will have access to these records/data.

A copy of de-identified fMRI images, with no participant names, dates in date fields, or other

VASI, will be kept on a VASDHS contracted (initial contract #: 36C26218C0160) computer server in the west datacenter of San Diego Supercomputer Center (SDSC UC San Diego MC 0505, 9500 Gilman Drive, La Jolla, CA 92093-0505). This storage solution complies with all VA directives developed in accordance with FISMA, HIPAA, NIST, and related VA security and privacy control requirements for Federal information systems. This includes standards for the protection of electronic PHI, outlined in 45 C.F.R. Part 164, Subpart C, information and system security categorization level designations in accordance with FIPS 199 and FIPS 200 with implementation of all baseline security controls commensurate with the FIPS 199 system security categorization (reference Appendix D of VA Handbook 6500, VA Information Security Program).

VMRF laptop computer will be used to collect non-sensitive behavioral data (664 EE111331). A copy of all behavioral data will be transported to the R drive using VA-issued encrypted thumb drive and stored permanently on R:\Crocker.

27.4b2) Identify precisely where ***VASI*** electronic records/data will be stored to include the full map drive, network location/server name, etc., and a brief description of what data/information is stored at each location.

If no VASI is collected or recorded for this study, simply indicate that the "Study does not collect or record VASI".

An additional storage location will be the R drive on the secure VA network, specifically folder R:\Crocker for VASI electronic data.

VASI data, coded with a participant ID number, will be stored through the VA REDCap system, which is only accessible on a VA computer network with a VA login. Data exported from REDCap will be encrypted and stored on the R drive. Only essential study personnel will have access to these records/data. Once data collection is complete, the data will be exported from REDCap one last time and then the REDCap database will be deleted.

27.4b3) Are any of the locations described in 27.4b outside of the VA Secure Network? *Note: this includes storage on a computer local hard drive.*

○ Yes ◉ No

27.4c) Record Retention - VHA requires compliance with Records Control Schedule (RCS-10) for retention of electronic and hard copy records. Following study closure, these temporary records must be retained for six years and then destroyed. Longer retention may be permitted if requred by other Federal regulations or requirements. Will RCS-10 requirements be followed (i.e., 6-year retention)?

◉ I will adhere to VHA Records Control Schedule-10 requirements
○ I request an exception to RCS-10 requirements

Section 27.5 Additional Privacy or Information Security Details

Provide any other privacy or information security details here.

A portion of the treatment sessions will be audio recorded to be reviewed by VA study staff to ensure treatment fidelity. The digital audio recordings will be uploaded to the "R:\Crocker" folder and deleted from the digital recorder immediately after upload. The digital recorder will be stored in a locked cabinet in building 13, room 312H when not in use. Audio recording will only take place if study participants have agreed to audio recording and have signed the VA consent form. Recordings will be destroyed following RCS 10 guidelines.

For the cognitive training portion of the study, data transport and storage systems are HIPAA and FIPS-140 compliant. No personally identifiable information is mandatory to use the BrainHQ program. User names may be coded as anonymized study identification numbers or otherwise de-identified. The only information created, transmitted, and stored by the program pertains to usage (e.g., how much training has been done) and progress (e.g., how much improvement has been calculated) that a user makes. IP addresses are not recorded to be in HIPAA compliance.

Section 27.6 Attestations

In the event of real or suspected breach of security, the Information Security Officer, Privacy Officer, VA Police (if appropriate), and the individual's supervisor will be notified within one hour of learning of the event.

(•) Agree ( ) Disagree

Study staff will be up to date on any required VHA Privacy Policy and Information Security training or they will not be allowed access to VA Sensitive Information.

(•) Agree ( ) Disagree

Access to research sensitive information, if any, will be removed when study personnel are no longer part of the research team.

(•) Agree ( ) Disagree

At least one copy of all study records (whether sensitive or non-sensitive) will be retained under VA control and only destroyed in compliance with the approved Records Control Schedule

(•) Agree ( ) Disagree

The VA retains ownership of the research data. Should the investigator leave the VA, custody of the research records will be assigned to another investigator and the Research Service notified in writing, or custody of the research records will be transferred to the Research Service.

(•) Agree ( ) Disagree

Section 28 - Protocol Association to New or Existing Project

28) Is this a new R&D Project? Before you go on to complete the *Initial Review Submission Form* (which is used for attachments), please address the association of this Protocol to an R&D Committee Project. This Protocol may represent a new R&D Project, or it may be an additional Protocol under an existing R&D Project (such as when a single grant supports multiple Protocols). Will this Protocol be submitted to the R&D Committee as a new Project?

(•) Yes ( ) No

The Protocol Application is now complete for a Protocol that will also be a new R&D Committee Project.

Next you will go on to the Initial Review Submission Form which is used to package up the Protocol Application and any needed attachments and submit them to the IRB.

Click on *Save and Continue*