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EFFICACY AND NEURAL MEDIATORS OF RESPONSE TO TRAUMA MANAGEMENT THERAPY FOR PTSD

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EFFICACY AND NEURAL MEDIATORS OF RESPONSE TO TRAUMA MANAGEMENT THERAPY FOR PTSD

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PURPOSE/OBJECTIVES:

This research is intended to provide data from humans to test the efficacy and examine the neural mediators of response to Trauma Management Therapy (TMT) among veterans with post-traumatic stress disorder (PTSD).

In this study, our specific aims are to 1) test the efficacy of TMT for the treatment of fear and anxiety symptoms of PTSD as well as the interpersonal dysfunction associated with PTSD, and 2) identify neural mediators of TMT-related reductions in fear and anxiety as well as interpersonal dysfunction in veterans.

Treatment-seeking veterans with PTSD will be randomized into one of two treatments: (i) *Trauma Management Therapy*, consisting of 12 individual sessions of exposure therapy and 24 group sessions of social and emotional rehabilitation, or (ii) *Prolonged Exposure Therapy (PE)*, consisting of standard 12 sessions of exposure therapy and 24 group sessions of skills-focused group therapy based in acceptance and commitment therapy (ACT) and dialectical behavioral therapy (DBT). Clinician-administered and self-report measures of (i) fear and anxiety symptoms of PTSD, and (ii) interpersonal dysfunction associated with PTSD will be assessed across the course of treatment. We will test the primary hypothesis that the addition of social and emotional rehabilitation to the standard course of exposure therapy leads to greater reduction in interpersonal dysfunction, and evaluate potential neural mediators of efficacy.

Veterans enrolled in in the study will undergo functional neuroimaging as they engage in an emotional image viewing task, as well as two social interaction tasks sensitive to aggression and cooperation. The neurobehavioral assessments will be made prior to and following completion of treatment. We will test the hypotheses that pre/post-treatment changes in the response of specific brain regions (detailed below) will mediate the relationship between TMT treatment and

reductions in 1) fear and anxiety during the emotional image task and 2) interpersonal dysfunction during the aggression and cooperation tasks.

BACKGROUND/PREVIOUS RELATED RESEARCH:

Post-traumatic stress disorder (PTSD) occurs in individuals who have experienced a significant trauma in which they (or someone close to them) were confronted with death or serious injury, or a shocking, scary, or dangerous event (1). The National Institute of Mental Health (NIMH) estimates that approximately 8 million American adults (age 18 and older) suffer from PTSD in any given year (2), and it is estimated that between 8% and 18.5% of veterans returning from Operation Iraqi Freedom/Operation Enduring Freedom/Operation New Dawn have been diagnosed with PTSD (3-5).

Interpersonal dysfunction, including anger and aggression, is a serious and frequent complicating factor in the treatment of PTSD. Interpersonal aggression and anger are: i) strongly associated with PTSD (6-7); ii) particularly pernicious among individuals with combat-related PTSD (8); and, iii) critical barriers to effective treatment in combat-related PTSD (9-10). Anger and aggression can also critically damage the interpersonal relationships of veterans; these relationships are essential to the social support necessary for recovery of functioning (11-24). Despite the detrimental impact that anger and aggression have on the lives of combat veterans with PTSD, and despite the barrier that anger and aggression pose to treatment and recovery, little attention has been focused on developing interventions targeting interpersonal dysfunction, or developing an understanding of neural mechanisms of treatment for interpersonal dysfunction. Accumulating evidence suggests that aggression may also be a significant moderator of PTSD treatment efficacy in both combat and peacekeeping veterans (9-10, 25). Exposure therapy remains the only modality of treatment with adequate evidence of treatment efficacy for PTSD (26-27), yet this treatment does not target or adequately reduce the interpersonal symptoms of combat-related PTSD, including anger and aggression, behavioral avoidance, impaired social functioning, and social skill deficits (28).

Treatment for Posttraumatic Stress Disorder in veterans

According to the Consensus Statement on PTSD by the International Consensus Group on Depression and Anxiety, **exposure therapy** is the most appropriate psychotherapy for PTSD, including both combat-related PTSD and military sexual trauma (29, 30). This conclusion was reaffirmed by the National Institute for Clinical Health and Excellence (31) and the Institute of Medicine (32). Exposure therapy, an effective and accepted intervention for a range of psychological disorders, operates on long-established and fundamental principles of behavior therapy and offers hope for alleviating acute symptoms of PTSD. Typically, exposure therapy is conducted using either imaginal or in vivo methods. Virtual reality (VR) as a means of augmenting exposure has been recently introduced into many treatment settings (33, 34) including the VA. VR is a particularly promising modality for treatment of veterans with PTSD, because in vivo exposure to traumatic events precipitating the onset of PTSD is not possible (e.g., car bombings, military sexual trauma). Furthermore, exposure using a VR environment overcomes a significant hurdle for many individuals with PTSD: an inability to engage in imagery of sufficient detail *and* affective magnitude to re-create essential aspects of the traumatic event. The use of VR may enhance the therapeutic efficacy for exposure, currently the only psychosocial empirically validated treatment

for PTSD. Such an innovation would increase the number of veterans who could be provided with services and who would benefit from this intervention. Early studies using "virtual Vietnams" have been effective in treating Vietnam War Veterans.

However, while there is a strong evidence base to support psychiatric interventions for the treatment of PTSD in civilians, there is a striking lack of corresponding evidence to support the treatment of PTSD in combat veterans (32, 35, 26). Moreover, exposure therapy may not address severe social impairment such as the "negative" symptoms of PTSD (e.g., avoidance, social withdrawal, interpersonal difficulties, occupational maladjustment, emotional numbing), or improve emotional regulation such as anger management (28). This is because exposure therapy is specifically focused on anxiety and fear reduction, and hence does not address other features of PTSD. Specifically, although exposure therapy may reduce maladaptive arousal and fear, it does not address basic skill deficits, help the veteran reestablish impaired relationships, address the problem of unemployment, or learn to control anger. Therefore, it appears that for a treatment to be fully successful, it must address not only the prominent problem of maladaptive anxiety and fear, but also the marked social impairment characteristic of PTSD in veterans.

Trauma Management Therapy (TMT)

Over the past 21 years, ongoing research has been performed to empirically validate Trauma Management Therapy (TMT), designed specifically to address the multiple aspects of chronic PTSD. TMT is an empirically supported multicomponent treatment program that combines traditional individually administered exposure therapy (29-30) with group-based social and emotional rehabilitation (36-38). Trauma Management Therapy is one of the first multicomponent treatments developed for the treatment of PTSD-related interpersonal dysfunction, as well as PTSD-related fear and anxiety. It is designed to specifically address the multiple aspects of chronic PTSD, which includes aspects of virtual reality (VR) assisted exposure and group social/emotional skills training.

TMT contains two treatment components. The first component is intensive individual exposure therapy, included to address the unique features of each veteran's fear. The second component is social and emotional rehabilitation, which uses a skills training formula and is conducted in small groups of 4-13 participants. This skills component was specifically adapted for combat related PTSD and is included to improve general social skills and help eliminate a number of specific deficits associated with PTSD. This treatment is not merely a combination of exposure and traditional social skills training. Rather, it includes content areas designed to remedy specific difficulties seen in veterans with chronic PTSD.

In an initial pilot efficacy trial of Vietnam-era veterans with chronic PTSD (N = 15), TMT was shown to yield a large pre- to post-treatment reduction in social withdrawal, in addition to reductions in nightmares, flashbacks, clinician ratings of general anxiety and other classic symptoms of PTSD (36). A second, randomized control trial in a similar sample of Vietnam-era veterans with chronic PTSD (N = 35), compared TMT to exposure therapy plus a psychoeducational group matched for number and duration of sessions (39). This RCT demonstrated similar and significant reductions in nightmares, flashbacks, clinician ratings of general anxiety and symptoms of PTSD for both TMT and the comparison treatment, exposure

with psychoeducational group. In addition, however, TMT yielded significantly fewer episodes of rage, significantly greater increases in time spend in social activities, and significantly greater increases in number of social activities engaged in, relative to exposure only. Based on these promising data, TMT represents a promising treatment that fills a significant gap in the treatment options available for veterans experiencing the debilitating effects of interpersonal dysfunction, in addition to the anxiety and fear associated with PTSD.

This study will utilize Trauma Management Therapy (TMT) in a residential program format, in which treatment will be delivered intensively within a shorter time frame, rather than a series of weekly outpatient appointments, where treatment stretches over several months and dropout rates are higher (40). The structure of this treatment is modeled on the Intensive Outpatient Program (IOP) format (40), which is designed to deliver treatment more rapidly, establish psychosocial supports for participants, and address relapse and enhance coping skills (41). Previous research suggests that exposure therapy is more efficacious when delivered in "massed" versus "spaced" fashion (42-43) as other programs that offer treatment once or twice per week typically have higher drop-out rates in these populations (up to 40%) (44-45). A recent study adapted TMT, a 29-session intervention administered across 17 weeks, to a three-week IOP format with a sample of 112 OIF/OEF/OND veterans, and the investigation showed a significant decrease in CAPS and PCL-M scores (indicative of PTSD severity) pre to post-treatment; decrease in illness severity (via the Clinical Global Impressions scale); and decreased sleep disturbance, anger, guilt, and depression pre to post-treatment (40).

Potential neural mechanisms of response to exposure therapy and treatment for interpersonal difficulties in PTSD.

Recent research indicates that genetic factors and specific regional brain structures may work in tandem to produce PTSD, or, alternatively, to act as protective factors against its development. Some of the elements that seem to be linked to individual stress reactions include the acquisition and extinction of fear responses, the amount of control over the stressor, and differential responses to emotional stimuli (46-48). Activity in specific brain structures has been shown to correlate with these elements.

The individual experience of trauma that is associated with PTSD can be related to a classical conditioning model of learning in which a previously neutral stimulus (US) is paired with an aversive stimulus (CS). After several such pairings, the US alone begins to elicit a fear response in the now-conditioned individual (49). In the case of PTSD, the severity of the trauma is such that the fear response is conditioned in only one pairing. Research using a classical conditioning paradigm in examining PTSD patients has shown that the amygdala plays a significant role in the acquisition of response to aversive stimuli. However, some investigators are now focusing on the extinction phase of learning, which seems to correlate with decreased activity in the rostral anterior cingulate cortex, leaving the role of the amygdala unresolved.

Previous fMRI studies using emotional faces have revealed differential neural activity in various brain regions in some psychiatric populations and healthy controls. Specifically, heightened amygdala response to negative stimuli compared with neutral stimuli has been found in some individuals with major depressive disorder and PTSD (50,51). In addition, PTSD patients exhibited

a decrease in cerebral blood flow in regions of the anterior cingulate cortex when presented with fearful emotional faces. Further, in a study of individuals with depersonalization disorder, who typically report emotional detachment, researchers found significantly decreased activity in the amygdala in response to stimuli with either positive or negative valence (52).

Exposure therapy for PTSD consists of repeated recounting of traumatic memories and the gradual approaching of trauma reminders (29,30). Through this process, veterans develop skills to manage and regulate emotional responses to trauma cues, and in doing so, gradually extinguish the fear associated with these traumas. Previous neuroimaging studies suggest that individuals with PTSD have impairments in neural circuits underlying the regulation of emotional responses, including over-active amygdala during the presentation or experiencing of trauma-related cues and decreased activation or a failure to activate ventral medial prefrontal cortex (VMPFC) (53). Despite the increasing focus on aggression and PTSD in the descriptive and treatment literatures, studies of the neuroscience of aggression in PTSD, and interpersonal dysfunction more generally, have been largely absent.

In prior work, our team has developed novel social interaction paradigms for the fMRI environment and, in over 140 OEF/OIF/OND combat veterans, identified mechanisms of interpersonal aggression, cooperation, and emotional dysregulation (54-56). Previous work by our group (56) and others indicates that hyper-reactivity in limbic structures and hypo-reactivity in ventromedial prefrontal cortex (VMPFC) distinguishes individuals with PTSD from those without (for review, see Etkin & Wager, 2007). Thus, we will first test the hypothesis that (i) pre/post-treatment changes in VMPFC and/or amygdala response during the emotional image task mediates the relationship between TMT treatment and reductions in ***fear and anxiety***. We have also identified neural correlates of aggression (amygdala and frontoparietal network) and cooperation (ventral striatum) within two-person social interaction tasks, in both healthy (54) and PTSD populations (55,57). Based on this work, we will test the *hypotheses* that (ii) pre/post-treatment changes in frontoparietal network and/or amygdala activity during an aggression task mediate the relationship between TMT treatment and reductions in ***interpersonal dysfunction***; and (iii) pre/post-treatment changes in striatal activity during a cooperation task mediates the relationship between TMT treatment and reductions in ***interpersonal dysfunction*.**

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SUBJECT INCLUSION CRITERIA

Male and female veterans of all ethnicities will be sought to participate. All participants must meet the following criteria during intake or analysis: 1) be between 18 and 64 years of age; 2) meet DSM-5 criteria for current Post Traumatic Stress Disorder, as assessed by study staff using the Clinician Administered PTSD Scale-5 (CAPS-5); 3) be fluent in English; 4) have vision corrected to be able to see a computer display clearly; 5) be able to provide informed consent and be able to follow verbal or written instructions; 6) assessed as not a significant harm to self or others.

SUBJECT EXCLUSION CRITERIA

All participants admitted to the unit will be allowed to partake in the study. Those with contraindications to the fMRI will complete behavioral only tasks. The following exclusion criteria will be applied to all participants during analysis: younger than 18 or older than 65; self-reported PTSD symptoms for less than six months; diagnosed seizure disorder; history of stroke; Cushing's syndrome; history of moderate to severe traumatic brain injury (TBI); electroconvulsive therapy within 5 years; history of chemotherapy for cancer; contraindications to fMRI; current pregnancy; diagnoses of schizophrenia, schizoaffective disorder, delusional disorder, organic psychosis, bipolar disorder, or depressive disorder with psychosis as assessed with SCID-5-RV (and not stabilized or in remission); symptoms meeting criteria for a substance use disorder within the previous 30 days (assessed through SCID-5, Alcohol Use Disorders Identification Test score > 8); meets criteria for acute psychiatric or medical admission; assessed as significant risk of harm to self or others; use of non-prescribed narcotics; acute cardiac difficulties (unless cleared by a cardiologist); psychotic disorders not otherwise specified assessed with SCID-5-RV; subjects using benzodiazepines (they will be given the opportunity to discontinue and must be off for at least two weeks prior to the beginning of the study); psychotropic medications must be stabilized for at least two weeks prior to the beginning of the study and remain stabilized throughout the entire duration of the study; if changed, the subject may be dropped from the study at the discretion of the research staff; positive drug tests during the course of the study will be grounds for disenrollment from the study. Given the high prevalence of psychotropic medication usage in

PTSD, use of antidepressants or anxiolytics will not be an exclusion criterion. The subject may be dropped from the study at the discretion of the research staff.

USE OF SPECIAL/VULNERABLE POPULATION:

For this study, we will be recruiting individuals with PTSD. As individuals with mental illness can be a vulnerable population, we will take particular care to prevent undue coercion, protect the subjects' confidentiality, and obtain informed consent. All subjects will be informed of the purpose of the study, the potential value of the study to society, the lack of value to the subject personally, and potential risks to the subject. It will be explained to the subject that he or she is under no obligation whatsoever to participate, and that if he or she wishes to discontinue involvement at any time during the study he or she is free to do so without penalty. Individuals receiving treatment for PTSD or any medical treatment from the VA will be assured that their treatment will in no way be affected by their choice to participate or not participate, or their choice to withdraw at any time.

STUDY DESIGN:

This study consists of two primary treatment groups: 1) Trauma Management Therapy, comprised of exposure therapy (EXP) and social and emotional rehabilitation (SER) (N = 44), and 2) veterans receiving Prolonged Exposure Therapy (PE), comprised of exposure therapy plus skills-focues group therapy based in Acceptance and Commitment Therapy and informed by Dialectical Behavioral Therapy (EXP + ACT/DBT) (N = 44). All participants will be recruited within the Salem VAMC residential PTSD unit, a 13-bed facility offering residential care for veterans with PTSD. The unit will exclusively offer one of the two arms of treatment (EXP+SER or EXP+ACT/DBT) at any particular time, and the order of offering will be randomized across the year. Thus, assignment to treatment arm will be depend upon the treatment arm being currently offered.

Individuals meeting inclusion and exclusion criteria will be invited to participate in the study protocol, consisting of a battery of neuroimaging tasks completed prior to and following completion of treatment. Individuals choosing to participate in the study will be asked to lie in an MRI scanner, located at the Fralin Biomedical Research Institute at Virginia Tech Carilion in Roanoke, VA, and play simple games consisting of viewing objects on a digital screen and making choices by pressing handheld buttons. The scanner detects regional cerebral blood flow accompanying changes in brain activation when subjects are perceiving emotional or reward-related stimuli. Subjects will be asked to participate in three tasks of this nature during the scanning session, depending on their comfort level and time available. Following the initial fMRI scanning session, participants will begin treatment (TMT or PE). Following completion of treatment, participants will undergo the above-described fMRI scanning procedures a second time.

PROCEDURES:

All research activities will be conducted by Salem VAMC research staff members at Fralin Biomedical Research Institute at Virginia Tech Carilion (FBRI) and/or Salem VAMC. The PI or

a clinically experienced senior staff member will accompany all subjects with PTSD throughout their participation in the study.

I. Recruitment

Veterans may learn of this study by being informed by residential clinical staff, receiving a letter from research staff at the Salem VA Medical Center (attached), word of mouth, or when inquiring about residential treatment at the Salem VA Medical Center. During the initial patient screening phone call for the PTSD residential unit, the VA staff member will also inform the patient of the study. If a veteran is interested in participating in research, study staff will contact him/her by phone to provide information about the study and conduct initial eligibility screening. In addition, letters will be mailed to Veterans who have expressed interest in the study. This letter (attached) will provide the Veteran with the contact information for study staff. At the request of clinical PTSD RRTP staff, a letter (see attached) including a description of the study and contact information for study staff will be provided to the PTSD RRTP clinical coordinator for the purpose of including it in each Veterans' clinical welcome packet.

Written informed consent will be obtained after the veteran is admitted to the Salem VA residential PTSD unit. Upon arriving at the Salem VA PTSD residential unit, individuals will again be given an overview of the study, including a basic description of the study design, and any questions they have will be answered. As part of the intake process within the unit, a variety of clinician-administered and self-report measures are completed to evaluate psychiatric symptoms and current psychosocial functioning, including the PTSD Checklist (PCL-5); Beck Depression Inventory (BDI-II); Posttraumatic Cognitions Inventory (PTCI); five facets of mindfulness; Insomnia Severity Index (ISI); Acceptance and Action Questionnaire (AAQ-2); and Disturbing Dreams and Nightmare Severity Index (DDNSI), etc (see attached for samples). S/he will be asked to consent to the use of the audio recordings of his/her clinical interviews during the research intake screening (SCID-5-RV & CAPS-5), and of his/her individual therapy sessions, so that the reliability of assessment procedures and treatment fidelity can be evaluated. In addition, s/he will be asked to give permission for research staff to access intake assessment information and medical record history, in order to further evaluate eligibility criteria for the study.

Interested veterans will also be asked to complete a pre-consent MRI screening form (attached) over the telephone during their initial phone screen with study staff. If contraindications to MRI involving potential metal are identified (e.g. shrapnel, medical devices, etc.), veterans will be instructed to request a written note from their medical provider stating that any metal in their body is MRI safe. A radiologist from Salem VAMC may evaluate the safety of the veteran to participate in the study, should he or she desire to participate. If a participant is ineligible to participate in the MRI portion of this study, they may participate in the rest of the study and complete the tasks outside of the scanner.

Individuals who remain eligible for the study following clinical intake assessments, research intake assessments, review of medical record and assessment for contraindications to MRI will be invited to participate. Once the participants complete all pre-treatment study procedures, all participant data will fall under intention-to-treat analysis, where dropouts and non-compliant participants may be followed up on with post-treatment assessments and follow-up assessments as with all other

participants. Veterans who are found to not meet inclusion criteria following pre-treatment assessment may be unenrolled from the study at the discretion of study staff. All Veterans who are removed from the study will be paid for all study procedures completed to that point.

Veterans who may be eligible for Neuroscience of Social Behavior (PC-0002) study will be asked to complete a Release of Information form to share their contact information with PC-0002 study staff. A copy of relevant de-identified assessment data (see attached list) may also be released to the PC-0002 staff once written informed consent has been obtained by them from the Veteran.

The research staff will explain the study to the veteran and will answer any questions he/she may have prior to obtaining written informed consent.

Veterans will be assured that their choice to participate, or not, will have no effect on their treatment, clinical care or relationship with their clinician.

II. Assessment and Intervention

Initial Visit: Consent and Pretreatment Procedures
After written informed consent has been obtained, participants will begin study procedures.

Participants will complete pretreatment interviews, including the CAPS-5, SCID-5-RV with a trained clinical interviewer prior to beginning treatment.

Participants will complete the study questionnaires on paper during the first week at FBRI and/or at the Salem VA Medical Center (questionnaire battery including, for example, PCL, SAS-SR, AQ, ITS, etc.). Additionally, acceptability of treatment will be assessed through measures of treatment credibility and satisfaction after three weeks of treatment and the end of treatment, respectively.

The participant will be transported via VA vehicle or their own transportation arrangement from the PTSD residential unit at the Salem VAMC to the Human Neuroimaging Lab at the Fralin Biomedical Research Institute (FBRI) at Virginia Tech Carilion for the pre-treatment fMRI scanning/task visit. If the participant chooses to be transported via VA vehicle, they will be accompanied to the FBRI by trained research staff member who has been VA-approved to transport veterans.

Identifiable data (MRI screening form and Informed Consent form) will be transported by authorized study staff outside of the VA to the Fralin Biomedical Research Institute at Virginia Tech Carilion during the fMRI pre- and post- treatment scanning visits via a secure, locked VA document bag in the VA vehicle. This identifiable information will not be stored or housed off-site. All identifiable information will return directly to the Salem VAMC in the VA vehicle with the authorized study staff following the scanning visit(s).

Following consenting procedures and transporting the participant via VA vehicle to the FBRI, study staff will review safety issues related to MRI with the subject and answer any questions the participant may have. The primary procedure for this portion of the study is an MRI scan. The

MRI scanner is a 3.0 T scanner, approved for clinical use by the FDA. For subjects with PTSD, a clinically trained staff member will be available throughout the experiment to assist the veteran if he/she becomes agitated, frightened, or hostile.

In an effort to reduce the possibility that subjects will be adversely affected by the scanner noise or the visual or auditory stimuli, subjects will be shown sample stimuli to be used in the task (see attached). Before they are presented, the experimenter will briefly describe the sample stimuli and inform subjects that they can decide either to view or not view the stimuli. In addition, short clips of representative scanner sounds and volume will be played prior to the participant entering the scanner.

After being presented with the representative stimuli and hearing scanner sounds, participants will again be asked whether they want to continue with the study. They will be informed that they still will be compensated for their time if they choose not to complete the scan. Should the participant indicate they wish to discontinue the study, the study will be terminated at no penalty to the subject.

At each fMRI scanning session, the subjects will lie still for up to 35 minutes while in the scanner. Individuals will have the opportunity to get into and out of the scanner between each task described below. As with conventional scanners, the subject in the scanner will be in voice-communication with a technician, clinically experienced staff member, or investigator via an intercom and will have an emergency squeeze bulb in case he/she wishes to be withdrawn.
Participants will be asked to perform some or all of the following tasks depending on their comfort and time available. For all the scanning tasks, participants will view a computer display positioned at one end of the scanner by looking into a mirror positioned above their head. They will also use handheld buttons similar to a computer mouse to make choices during the games. If the participant is not MRI-eligible, they will complete these tasks on desktop computers outside of the scanner.

Task 1: Interpersonal interaction: The participant will play an exchange game with a human partner who has also joined the study, or a 'computer' partner that has been preprogrammed to play the game. The experience of the game will be similar to a standard, commercial video game, except with much simpler images. While playing the game, subjects will view stimuli representing their options and choices (e.g., an unmarked card and a slider bar indicating a choice of $10). Choices will be made by pressing buttons on a button box. Subjects will be compensated, in part, based on their earnings in the exchange game in order to incentivize performance. The duration of this task is approximately 30 minutes.

Task 2: Cue / emotional-reactivity task: This task assesses neural signals associated with responses to simple visual stimuli. Participants will view or hear generic stimuli (e.g., colors, words, symbols, sounds or images drawn from standard stimulus sets such as the International Affective Picture System; IAPS, Lang et al., 1995; International Smoking Images, Gilbert; International Affective Digitalized Sound System, IADS, Bradley & Lang, 1999) as they are asked to make evaluative judgments (e.g., preference, duration, valence ratings) or passively view the stimuli. The duration of this task is approximately 15 minutes.

Task 3: Social Status/Aggression task: During this task, the participant will play an exchange game with a human partner who has also joined the study, or a 'computer' partner that has been

preprogrammed to play the game. While playing the game, subjects will view stimuli representing their options and choices (e.g., slider bar indicating a choice of $10). Conditions of certain game variants may include one subject challenging his/her partner at a monetary cost to him/herself. Subjects will be compensated, in part, based on their earnings in the exchange games in order to incentivize performance. The scanner will detect changes in regional cerebral blood flow that accompany neural activity during these tasks. The duration of this task is approximately 30 minutes.

Following completion of the imaging/task session, each participant will be transported via VA vehicle or by their own transportation arrangement from the Human Neuroimaging Laboratory at the Fralin Biomedical Research Institute at Virginia Tech Carilion back to the PTSD residential unit at the Salem VAMC.

Psychotherapy Interventions

Treatment will be conducted by Master's or doctoral-level clinicians at the Salem VAMC. All therapists will be trained and experienced with behavioral treatments for psychological disorders, including PTSD. In addition, therapists will undergo 20 hours of clinical training: 10 hours of didactics and discussion, and 10 hours that will consist of running one mock group through each TMT phase and component, and one individual session where an imaginal scene is constructed and administered to a mock patient. Training will be conducted by TMT experts/creators (Deborah Beidel, PhD & Christopher Frueh, PhD), who will be involved in ongoing supervision and consultation throughout the project. Treatment sessions will follow the manual constructed for TMT and therapists will be supervised in weekly sessions (including the use of recordings of sessions). When problems of adherence or quality are detected, reeducation will occur. We will have adherence data at the end of treatment such that determination of overall adherence can be made.

This study includes two treatment arms, described below. Both treatment arms will be administered across 6 weeks, and the TMT group will include 12 sessions of individualized exposure therapy (EXP); while the PE group will have 12 sessions of individualized exposure therapy. The treatments will also differ, in that Trauma Management Therapy will include 24 sessions of group-based sessions targeting social and emotional rehabilitation (SER), while the control condition will include 24 sessions of skills-focused group therapy (ACT/DBT).

a) **Trauma Management Therapy (EXP+SER)**: TMT will consist of 36 treatment sessions administered over a period of 6 weeks, including 12 sessions of individualized exposure treatment (EXP) and 24 sessions of group-based social and emotional rehabilitation (SER). Two sessions of exposure therapy and four to six sessions of group therapy will be completed each week. Exposure is implemented individually, while SER is administered in small group sessions (up to 13 people). Both exposure and group treatment sessions average 90 minutes per session, which results in approximately 58.5 hours of therapist contact for each patient. Therapist-led individual in vivo exposure sessions will also be conducted by clinical staff as part of standard TMT and will provide additional hours of therapist contact for each patient. These sessions prepare the veteran for successful Programmed Practice (described below).

TMT is a multicomponent behavioral treatment program designed to target various aspects of chronic PTSD - reducing emotional and physiological reactivity to traumatic cues, reducing intrusive symptoms and avoidance behavior, improving interpersonal skills and emotion modulation (e.g., anger control), and increasing the range of enjoyable social activities. TMT consists of several interrelated components: education, intensive exposure, social and emotional rehabilitation, homework assignments, flexibility exercises, and programmed practice. The major components of TMT are detailed briefly below.

(1) Education. This information is presented in the first treatment session. All participants are provided with a general overview of chronic PTSD, including common patterns of expression, issues of diagnosis, comorbidity of other disorders, etiological pathways, and a review of current treatment strategies. This phase ensures that participants not only develop a realistic understanding about treatment prognoses, but also an overall positive expectancy regarding treatment efficacy. Also, this phase educates participants about TMT and the expectations for treatment.

(2) Exposure Therapy. Individually administered intensive exposure is administered first because it effectively addresses the unique features of each participant's fear structure. We will use virtual reality based intense exposure, as it appears that adding this element may substantially augment traditional exposure procedures (e.g., it overcomes a significant hurdle for many individuals with PTSD - an inability to engage in imagery of sufficient detail *and* affective magnitude to re-create essential aspects of the traumatic event). We will use the "Virtual Iraq" program designed by Virtually Better, in Atlanta, Georgia, for this project. In addition to a realistic visual, aural, and tactile environment, this program includes the ability to present scents that have been known to trigger PTSD symptoms in these participants. For veterans who have not experienced traumatic events consistent with the virtual visual environments, other aspects of the virtual reality system (e.g., scents or sounds) will be utilized as appropriate. By combining these four sensory modalities, we will be more likely to engage the traumatic fear memories and thereby extinguish the associated fear responses. The goal of exposure is to provide prolonged contact with the feared stimuli of sufficient duration that within session habituation occurs. Exposure consists of 15 individually administered sessions. All intense exposure sessions are conducted for 90 minutes of presentation, with reactivity monitored physiologically (i.e., heart rate) and by patient ratings of subjective distress. Sessions are terminated when the participant reports low subjective distress and any simulator sickness symptoms have subsided.

(3) Programmed Practice. The programmed practice component of TMT is implemented as part of the final 7 individual exposure sessions, and is a form of exposure that does not necessitate therapist–accompaniment (i.e., it is "homework"). Homework assignments, like exposure sessions, are geared specifically toward the participant's individual fear pattern. Examples of suitable assignments include watching movies (e.g., *Platoon* or *Hamburger Hill),* visiting war memorials or museums, speaking with other participants or loved ones about war experiences, and visiting airfields or helicopter pads. Experiences should also be devised which require the participant to engage in other feared activities, the avoidance of which may interfere with his or her quality of life. Examples of suitable activities include social events (e.g., parties, having dinner with friends), shopping, attending movies, eating in a restaurant, etc.

(4) Social and Emotional Rehabilitation (SER). This component is conducted in a group modality and will consist of up to 13 participants and one to two clinicians. A highly structured group administered SER component was developed to target the interpersonal difficulties that are often part of PTSD but are not improved by exposure only. These difficulties include social anxiety, social alienation and withdrawal, excessive anger and hostility, explosive episodes, marital and family conflict. SER is implemented in small group sessions and includes basic social skills training, anger management and behavior activation therapy. Components of SER are as follows:

Brief behavioral activation. In brief behavioral activation (Lejuez, Hopko, Acierno, Daughters, & Pagoto, 2011), veterans learn skills to deal with depression and guilt. Treatment involves identifying areas of functioning where the individual would like to make changes and examining the values held within those areas. Across two sessions, 10 life areas are examined: family relationships, social relationships, employment/career, physical and psychological health issues, responsibilities, romantic relationships, education/training, hobbies/recreation, volunteer work/charities/political activities, and spirituality. After identifying areas where change is desired, the patient identifies and plans daily activities that are consistent with the values identified as important. Accomplishing activities that are closely linked to core values results in more positive and enjoyable experiences, which in turn improves perceptions and cognitions about life. Behavioral activation for depression was not included in the first iteration of TMT (Beidel et al., 2011), but it is now an integral component of social and emotional rehabilitation as a result of the depression and guilt so often expressed by OIF/OEF/OND veterans (Strachan, Gros, Ruggiero, Lejuez, & Acierno, 2012).

Sleep hygiene. Sleep difficulties are a common complaint by people with PTSD. In SER, three sessions are devoted to sleep hygiene. The content includes learning various aspects of the sleep–wake cycle, concepts such as sleep efficiency, and how behaviors such as inconsistent sleep times, napping, and drinking alcohol can interfere with sleep and affect sleep efficiency. Patients are instructed in the use of a sleep tracking/monitoring form, which is used in the next session as the basis for the instruction in better sleep hygiene, including sleep scheduling, avoiding foods and drink that increase wakefulness, creating a bedtime ritual, setting up an environment conducive to sleeping, limiting daytime naps, exercising, and managing stress.

Anger management. In the three anger management sessions, the focus is on teaching the patient how to better manage anger and other intense emotions. It is designed to reduce temper outbursts and the problematic expression of anger. This component gives veterans a range of strategies for emotional expression. One topic (anger management, problem solving, and guilt) is introduced at each session, and a short didactic presentation is followed by practice in the implementation of skills using role playing, worksheets, and group discussion. With respect to anger management, the skills are broken down into specific components, which include identifying high- risk situations and planning ahead, taking a break during a heated moment, reevaluating the situation, problem solving (which is expanded upon in a subsequent anger management session), and using assertive communication. Problem solving skills include defining the problem, brainstorming, evaluating solutions, and selecting/implementing a solution. One exercise uses a “responsibility pie” to address guilt related to certain traumatic events, and steps include assessing the seriousness of the actions, weighing personal responsibility, breaking the “guilty silence,” self-forgiveness, and making reparations.

Social reintegration. These sessions teach how to establish/ reestablish and maintain friendships, skills necessary to engage in and maintain new and diverse social activities or to reestablish strained interpersonal relationships with family, friends, and coworkers. Specific attention is given to assertiveness skills, teaching appropriate methods of expressing anger or requesting behavior change. Skills are taught using a traditional social skills format using modeling, behavior rehearsal, and feedback.

Integration session. This session allows patients to pull together the material from the various sessions, allowing integration of problem solving, assertiveness training, and social reintegration, for example. Therapists sometimes use this session to provide additional practice in a specific skill or area that appeared problematic for a particular group.

Relapse prevention. In these sessions (during the sixth and final week of treatment), group leaders will help veterans integrate the skills they have learned in each area into a relapse prevention plan for returning home. This will include identifying situations/events/ people that might serve as triggers for a return to behaving inappropriately in formerly problematic situations are discussed and alternative responses are discussed. Efforts to decrease general levels of arousal that might be unrelated to PTSD are presented (e.g., relaxation training, exercise) are discussed, depending on the needs of the individual group.

(b) **Prolonged Exposure Therapy plus Skills-Focused Group Therapy based in Acceptance and Commitment Therapy and Dialectical Behavioral Therapy:** Participants assigned to this condition will receive 12 standard sessions of individual PE consisting of imaginal exposures. Independent in vivo exposures are also assigned as part of standard PE. PE is currently the primary treatment provided at the Salem VA Medical Center PTSD residential unit. Standard PE does not utilize virtual reality; therefore, all exposure sessions will be imaginal and in vivo for this group. Participants will simultaneously attend group therapy consisting of the standard Salem VA PTSD-RRTP group treatment that provides psychoeducation and skills training based in ACT and DBT (e.g., psychoeducation about PTSD and emotions, emotion regulation, nonjudgmental mindfulness, and distress tolerance skills). Subjects in the PE condition will not receive the SER groups provided by TMT.

Post-Treatment fMRI Scanning Visit
Participants will be invited to complete post-treatment interviews (i.e., CAPS-5 & SCID-MDE), questionnaires, and fMRI scanning visit following completion of TMT or the control arm (PE). The procedure at these visits will follow the protocol as outlined in "*Initial Visit: Consent and Pretreatment Procedures*" (above). In the event that a participating Veteran discharges from the PTSD RRTP prior to completion and is unable/unwilling to travel back to the Salem VAMC and/or FBRI for the posttreatment procedures, study staff may complete the posttreatment interview and/or questionnaire portions over the telephone.

Follow-up
In addition to the post-treatment scan/assessment all participants will be assessed via telephone or in-person at 1-week, 3- and 6-months post-treatment (questionnaire battery including, for example,

CAPS-5, PCL, SAS-SR, AQ, ITS, etc. [see attached for samples]). Each participant will receive a packet of assessments/questionnaires to take home with them after treatment. During the follow-up sessions, study staff will call the participants to have them open the packets and complete the assessments/questionnaires with a staff member over the phone so that the study staff are available to answer questions. If study staff is unable to reach the subjects over the phone or the subjects are unable to complete the questionnaires over the phone, they may be asked to complete the questionnaires on their own and mail them back to study staff. The packet will include postage-paid envelopes for the participants to mail their completed questionnaires back to the Salem VAMC. These questionnaire packets will not contain any PHI or PII. Reminder letters for follow up appointments will be mailed to participants prior to the appointed assessment time (see attached). Veterans will receive reminder phone calls and letters (attached) prior to follow up appointments. Any patients who are terminated from or drop out of the study during treatment will also be assessed via telephone at 1-week, 3- and 6-months post-treatment. Those who develop other acute problems during follow-up will be referred to other appropriate treatment providers. Records will be kept on relapse and emergence of new problems, including the nature of the problems, the circumstances under which they developed, and the kind and amount of treatment received.

Participants who are not considered significantly improved after the six-month follow-up (non-responders) will be referred to appropriate clinical treatment for residual problems such as depression or grief. Patients who relapse, as defined by (1) exacerbation or return of symptoms such that PCL ratings return to or are above (worse than) baseline levels; or (2) the functioning deteriorates to the point where acute psychiatric hospitalization is necessary to ensure patient safety. All subjects will also be given the study psychologist's and/or research coordinator's contact information and will be encouraged to call the lab if they are experiencing any difficulties in the hours, days, or weeks following their participation.

SAMPLE SIZE:

Our goal is to have 44 subjects in each of the two treatment groups complete this study over the course of four years. From our past experience conducting studies of this complexity with specific inclusion/exclusion criteria, we anticipate needing to enroll 1.5 subjects to achieve 1 subject who meets criteria and finishes the study. Thus, we multiplied our target of 88 subjects by 1.5 to reach our total sample size of **132**.

PROVISIONS FOR MANAGING & REPORTING ADVERSE EVENTS:

During all phases of the study, a doctorate-level clinician will be available for consultation and to help manage any negative reactions that occur in response to the neuroimaging sessions. All study staff working with the patients will be trained in suicide risk assessment, basic suicidal crisis intervention skills, and the study's safety protocol.

If patients exhibit symptoms of significant distress or anxiety at any time during their participation in study procedures at FBRI, they will be guided through clinical techniques to help them regulate their distress. Their session may be terminated if deemed appropriate. If it is determined that they are expressing suicidal/homicidal ideation or thoughts of self-harm or harm to others, clinically

trained staff will work with the veteran to reduce distress and/or acute suicide or homicide risk. When the veteran feels calm and is determined by staff to not be an imminent risk to self or others, they will be escorted back to the residential unit by a trained research staff member via the VA vehicle. If a veteran has driven or ridden in a private vehicle to the appointment and the veteran is deemed stable and safe by staff, they may be allowed to drive their vehicle back to the Salem VA and check in to the residential unit. If at any time clinical staff determine that the Veteran is an imminent risk to self or others and/or not safe to independently drive or ride in a private vehicle, the Veteran will be transported via the VA vehicle or ambulance, whichever is clinically indicated. Study personnel will remain with patients determined to be an imminent risk to self or others until direct hand off to a VA clinician or EMS response is possible.

Additionally, Drs. Casas or Chiu will be alerted immediately and study staff will brief the veteran's VA clinician. If the Veteran has experienced distress but is stable, study staff will notify the patient's VA clinician immediately by telephone or pager. If the veteran must be transported via ambulance, study staff will notify the VA ED, nursing staff on the residential unit, and the Veteran's VA clinician. If the veteran has expressed homicidal ideation or intent to harm others, security staff will be notified.

For an Information Security or Privacy incidents, suspected or actual, the ACOS for Research, Privacy Officer and Information Security Officer are notified within 1 hour of discovery.

CONSENT PROCEDURES:

If individuals entering the PTSD residential unit are potentially eligible to participate, based on the phone screen and review of intake assessments, the research project will be explained, and any questions that potential participants have will be answered by study staff. Individuals expressing interest in participating will be asked to complete a pre-consent MRI screening questionnaire that evaluates contraindications to magnetic resonance imaging. For those who completed the MRI screen over the phone with study staff, they will be asked to review their MRI screening form and update if needed. If there are any concerns about a veteran's safety for MRI procedures, the veteran may be asked to complete X-rays to ensure the absence of metal. Veterans will be informed there is no charge for any X-rays and will be reminded that they may decline to participate in the study at any time. A radiologist at Salem VAMC will review the veteran's chart and x-rays and will make the final determination concerning the safety of the subject's participation in the fMRI for research purposes.

Individuals who remain eligible for the study following intake assessments, review of medical record and assessment for contraindications to MRI will be provided with a study consent form to review. Subjects will be given a quiet place and ample time to review this form independently. A study staff member will also review the contents of the consent form with each potential participant and answer any questions the participant may have prior to providing consent. The study staff will be sensitive to cultural, educational, or language difficulties and will ensure that the subject adequately understands the procedures, benefits, and risks of the study and has the capacity to provide informed consent prior to proceeding with the study. Informed consent will be obtained in writing on the study's consent form that will be stored in a secure locked cabinet for the duration of the study. The subject also will be provided with a copy of the consent form.

If participants are ineligible for participation based on their screening information or choose not to participate in the study, initial screening information linked to subject identity will be destroyed upon completion of the study. The initial screening information will be kept until completion of the study to ensure that the same person is not screened for participation more than once. Study staff will emphasize to all participants that they may withdraw from the study at any time with no adverse consequences and will be compensated for their participation in the study up to that point.

In response to COVID-19, participants who have been accepted into the PTSD unit and passed the initial phone screen will be mailed informed consent and HIPAA forms via FedEx, USPS or UPS. Study staff will follow up with the interested Veteran via phone or VA Video Connect to (1) confirm they have received and read the ICF and HIPAA form, (2) answer any questions the Veteran may have, (3) provide instructions for filling out the forms, and (4) have the Veteran complete and sign the forms while on the phone. The Veteran will then be instructed to mail the forms back to study staff using the provided envelope and label with tracking.

After study staff have received the signed ICF and HIPAA forms, they will contact the Veteran via telephone or VA Video Connect to conduct the pretreatment interviews (SCID and CAPS) to establish final study eligibility. No study procedures will be conducted prior to receiving signed informed consent and HIPAA forms. Interviews will be scheduled as close to estimated admission as possible. Should the time elapsed between the interviews and admission surpass 2 months due to delayed admission, interviews will be readministered to ensure data validity.

For eligible Veterans who are enrolled, informed consent will be reviewed and confirmed via the established in-person procedure after admission to the PTSD unit. This will occur when normal research and clinical procedures are restored.

Veterans who have been accepted to the PTSD unit and have passed the initial study phone screen may be invited to complete the informed consent process in-person if they are staying locally prior to being admitted to the unit. Once informed consent has been obtained, study procedures such as the pretreatment interviews, questionnaires and/or scans may also be completed. Study procedures will be conducted during the week prior to the Veteran's planned admission date. If a Veteran subsequently defers or declines admission to the PTSD residential program, they will be unenrolled from the study, but may participate at a future date. No study procedures will be conducted prior to obtaining informed consent.

Similarly, Veterans may be invited to complete posttreatment interviews, questionnaires and/or scans if they are staying locally after discharging from the PTSD unit. Study procedures will be conducted as close to discharge as possible and not past the week following discharge.

In some cases, Veterans may be offered travel and/or accommodation resources if they wish to complete study procedures in-person prior to their admission and/or after discharge from the unit. No study procedures will be conducted prior to obtaining informed consent. These resources will be funded by the National Institutes of Health under Award Number UL1TR003015. Funds from this award will be managed and distributed by the integrated Translational Health Research Institute of Virginia (iThriv), which is a NIH funded program hub that aims to accelerate health

discoveries and improve health outcomes for all people. Funds will be used directly to pay for these offered resources i.e. the funds will not be distributed to the study staff or to the Veterans.

Veterans wishing to use these resources will be asked initially for their verbal consent to releasing their name and phone number to the iThriv partnership manager for the purposes of booking their travel or accommodations. Upon arrival to their in-person research session, they will be asked to sign the VA Form 10-5345 (Request for and Authorization to Release Medical Records or Health Information). Demographic information such as race, sex, ethnicity and race will also be requested to be released to the iThriv program for NIH grant reporting purposes.

COST/COMPENSATION:

During the course of this study, no medical procedures will be performed and no insurance companies will be billed. All expenses incurred in performing the study will be paid for by the VAMC. Subjects will be compensated for their participation in the fMRI visits of the study; for the transportation time between the Salem VAMC and the FBRI to complete the fMRI visits; and for the 3 and 6-month follow-up assessment sessions. Subjects will be paid after each assessment portion of the study protocol (i.e., pre-treatment, post-treatment, 1-week, 3-months, and 6-months follow ups) via either direct deposit or check mailed from VA Financial Services. They will be informed that if they withdraw from the study at any time, they are still entitled to the compensation they have earned through that point in the study.

Assessment/questionnaire compensation:
For assessments and questionnaires that are not included in VA standard practice of care, such as CAPS-5, SCID-5, AQ, etc., the participants will be compensated according to a structured payment plan for completing each assessment session. See payment structure below in Table 1. Payment is based on the modal time required to complete each portion of the procedures at a rate of $15/hr. Some or all of these assessments will be completed over the phone one week after leaving the unit, and at 3-month and 6-month follow-up phone assessment sessions.

Task compensation:
For each task, participants will be compensated according to a structured payment plan (see Table 1 below). Payment is based on the modal time required to complete the scanning session at a rate of $30/hour if completed inside the scanner and $15/hour if completed outside of the scanner. Additionally, for the interpersonal interaction task (Task 1) and the social status task (Task 3), participants will be compensated based on their earnings in the exchange game in order to incentivize performance in addition to the hourly rate. Participants may also earn between $20 to $75 based on their performance on two of the MRI tasks.

Transportation compensation:
Participants will either be transported from the Salem VAMC to the FBRI to participate in the fMRI visits via a state vehicle or their own transportation arrangement. Parking at FBRI is free, so no parking compensation is required. The participants will be compensated a flat rate of $10 for roundtrip transportation. This rate is included in the total compensation for the fMRI visit;

however, in the event that a participant chooses to end an fMRI session early, they will still receive the full $10 transportation compensation.

Incomplete procedures/tasks:
Should participants choose to end any procedure early without completing it, they will be paid $15/hour for time spent, up to the scheduled payment for that procedure. As noted above, in the event that a participant chooses to end an fMRI session early without completing it, they will still receive the incorporated (and previously IRB approved) $10 compensation for transportation.

Unforeseen scanner-related delays:
Should participants encounter unusually long fMRI delays due to technical problems outside the control of the study staff, they may be paid $15/hour, at the discretion of study staff, for the duration of the delay to compensate for their time.

Participation bonus:
Participants can earn up to $40 in additional bonuses across posttreatment and follow up procedures conducted over the telephone, and those who participate in all portions of the study will receive a participation bonus of $50.

Participants can expect to earn a minimum of $170 for completing all portions of the study and a maximum of $700.

Payment Structure	
Pretreatment CAPS w/LEC	$30
Pretreatment SCID & SCID-MDE	$30
Pretreatment questionnaires	$30
Pretreatment fMRI	$45/90 (depending on in/out of scanner)
Task performance earnings	$20-75 (depending on performance)
Maximum Pretreatment total:	**$155-255**
Posttreatment CAPS & SCID-MDE	$30
Posttreatment questionnaires	$30
Posttreatment fMRI	$45/90 (depending on in/out of scanner)
Task performance earnings	$20-75 (depending on performance)
Maximum Posttreatment total	**$125-225**
1-week phone questionnaires	$10
Pre + Post + 1wk bonus	$20 (for completing all pre + post)
Maximum 1-week follow up total	**$30**
(Maximum Pre + Post +1-week total	***$310-510)***
3-month CAPS & SCID-MDE	$30
3-month questionnaires	$30
3-month completion bonus	$10 (for completing both)
3-month follow up total	**$70**
6-month CAPS & SCID-MDE	$30
6-month questionnaires	$30
6-month completion bonus	$10 (for completing both)
6-month follow up total	**$70**

Final completion bonus	$50 (if completed all procedures)
Maximum total possible earnings	***$500-700***

In order to compensate participants for task participation and transportation time, they will be informed that their name, address, social security number and bank account number (for direct deposit, if applicable) will be disclosed to the VA Financial Services. A deposit will be made directly into the participant's bank account unless he/she is unable to be reimbursed in this manner or does not wish to be; in which case a reimbursement can be made via a check, which can take 2-3 weeks to process. Due to limitations in the Financial Management System, payments made to participants through Austin Financial Services Center generate Internal Revenue Service Form 1099 regardless of amount of reimbursement. Participants will be informed that their SSNs will be used for this purpose in reimbursement.

If a research subject is injured as a result of participation in this study, under Federal Regulations, the VA Medical facility will provide necessary medical treatment. This does not apply to treatment for injures that occur as a direct result of non-compliance by a research subject with study procedures. Apart from medical care, no other form of compensation for injury will be provided.

CONFIDENTIALITY/PRIVACY PROVISIONS:

In order to protect the confidentiality of the data, subjects will be assigned a coded designation that does not include any personal identifiers. All paper records from the study will be identifiable only by this subject number and will be kept in a locked cabinet in a locked office (Room 132, Building 76 of the Salem VAMC). Electronic data will be accessed via password protected computer and secure server. Additionally, a digital key associating imaging data and behavioral data will be kept within a database on a secure network.

Information connecting the subject's identifying information with their assigned subject number will be accessible only by the study coordinator, PI, and immediate members of the PI's research team. All paper records containing identifying information will be kept in a locked cabinet in a locked office. The key for participant codes will be stored electronically in a restricted folder on the VA server only accessible to specific authorized study personnel This information will be stored in Tracy Hicks's office (Room 132, Building 76) at the Salem VAMC.

Electronic data will be stored in the PI folder (P:Research Records/King-Casas, Brooks) on the secure server. Only electronic data that has been de-identified will reside outside of the VA. This information will be stored securely on password-protected computers/servers.

In order to securely transport the fMRI screening forms, research consent forms, and HIPPA authorizations, the research coordinators or investigators will utilize a locked briefcase or bag to transport this material to and from the FBRI with the participant(s) in the state vehicle for the fMRI scanning sessions. They will personally transport the documents from FBRI to the Salem VAMC, where they will be stored in a locked cabinet in Tracy Hick's office. No identifiable information will be stored off-site.

Neuroimaging data, identified only by a code, will be stored on a hard drive equipped with FIPS 140-2 validated encryption located at the Fralin Biomedical Research Institute at Virginia Tech Carilion for the duration of the study. A FIPS 140-2 encrypted hard drive will also be used to securely transport an original copy of the data from the Fralin Biomedical Research Institute at Virginia Tech Carilion to the Salem VA Medical Center at the completion of the data collection phase of the study. If the VA-owned hard drive becomes corrupted or non-functional, it will be returned to the VA Office of Information Technology for appropriate destruction.

Audio data will be transferred from the audio recorders to the VA secured server (P:/Research Records/King-Casas, Brooks) regularly throughout the study by authorized study staff. The audio data will be located in a restricted folder only accessible to specific authorized study personnel for the purpose of treatment compliance auditing and assessment validity monitoring.

Members of the research study team that cease to be part of the project will have their access to study data removed. The research team will follow all VA rules and policies regarding the storage, return, and destruction of research records. Data will only be used by VA employees and will be used for the purposes of serving the purpose and objectives of the study listed above.

A Data Use Agreement is in place to transfer coded study data and limited individually identifiable information necessary for data analysis to a Virginia Tech IRB approved protocol (IRB# 20-438). This data will not be transferred prior to receiving approval from the VA IRB.

DATA AND SAFETY MONITORING PLAN:

All patient safety data will be reviewed weekly by the PI and study team. All treatment will be provided within the context of active case-management, so there will be excellent treatment infrastructure and clinical staff available to monitor participants throughout the treatment, appropriately address additional treatment needs, and handle crisis management should the need arise. Symptom status and presence of suicidal ideation will be monitored by project therapists at the beginning and end of every session using a short questionnaire to obtain subjective units of distress (SUDS) ratings for the domains of anxiety, depression, and suicidal ideation—scores of 7 or 8 (on a 0-8 scale) will require additional evaluation by project therapists before participants are allowed to proceed with treatment or leave the treatment session. Participants will be removed administratively from the study if their clinical status deteriorates such that it is judged to be in their best interest to receive treatment outside of the protocol. We will report all adverse events secondary to study involvement to the IRB.

Participants may be withdrawn from the study by the study investigator. Reasons for removal include noncompliance with the treatment protocol, worsening substance abuse, or other changes in mental or physical status that would prevent the participant from continuing in the study. Although participants may decline to answer certain questions during the assessment phase, they cannot refuse to participate in the treatment and remain in the project.

RISKS & BENEFITS:

Risks: The risks associated with fMRI are the same as those with conventional MRI. Movement or heating of metallic implants is a potential risk, and so subjects will be screened to exclude people with metallic implants, fragments, or pacemakers. Some individuals experience claustrophobic reactions in the scanner. Any subject experiencing claustrophobia will be removed from the scanner immediately.

There is no invasive component to this study, such as IV catheters, and so discomfort, bruising, or infection are not risks. The Siemens 3 T scanner has been approved by the FDA. However, there may be additional risks associated with scanning at 3 T compared to the conventional clinical scanners in the 1.5-2.0 T range. These include:

1. Effect of the static field. There is no conclusive evidence for irreversible or hazardous bioeffects to acute, short-term exposures of humans up to 2.0 T (Shellock and Kanal, 1996). Studies have indicated some side-effects at 4.0 T, namely unusual sensations including nausea, vertigo, and metallic taste (Schenck, 1991). However, there is no evidence that this is either irreversible or harmful. If subjects experience unusual sensations, they will be withdrawn.

2. Effect of the gradient field. MRI operates by rapidly changing small additional fields, called gradients. This will induce small electrical currents in any conductor, and thus could theoretically induce mild peripheral nerve stimulation. However, this is not substantially different at higher magnetic fields since the gradients are separate from the main magnet. There is no evidence that the effect of the gradients is any different at 3 T than at 1.5 T.
However, if subjects experience peripheral nerve stimulation, e.g. tingling or twitching, they will be withdrawn.

3. Effect of the RF electromagnetic field. The higher magnetic field strength requires that higher RF frequency pulses are used to excite the protons in the subject's brain. The limits of RF energy that can be safely given to humans has been clearly defined by the FDA: a. The exposure to RF energy below the level of concern is an SAR of 0.4 W/kg or less averaged over the body, and 8.0 W/kg or less spatial peak in any 1 g of tissue, and 3.2 W/kg or less average over the head; or b. The exposure to RF energy that is sufficient to produce a core temperature increase of 1 degree C and localized heating to no greater extent than 38 degrees C in the head, 39 degrees C in the trunk, and 40 degrees C in the extremities, except for patients with impaired systemic blood flow and/or perspiration. We will adhere to the recommendations for the head. The scanner has a large monitor indicating the RF power level which can be limited to a specific maximum.

While in the scanner, subjects will passively view emotional images and play exchange games with a partner. The duration of each task is 15-30 minutes, with a break between the tasks. The difficulty of the emotional task should be negligible and as no active response is required of the subject, there is no risk of physical strain. Subjects may, however, feel startled in response to some visual or auditory stimuli and the sound of knocking noises of the scanner. Similarly, the exchange task requires only minimal physical effort by the subjects when they press buttons to indicate their decisions during the game. The images are neutral in this task, but the subject may also feel startled by the scanner noise. If the subject experiences coughing or any other unpleasant sensation, the

subject may let the staff know via the continuous wireless intercom connection and/or emergency squeeze bulb we have in place, and the subject will be withdrawn immediately.

If a veteran screens positive on the MRI screener, the following steps will be completed to assess safety for research fMRI: 1) The PI or PI's staff will explain to the veteran that X-ray evaluation may be required to determine his/her safety for fMRI. The veteran will be given the opportunity to terminate participation at this time. 2) If the veteran chooses to continue the study, the PI or the PI's research coordinator will contact the radiologist who will review the veteran's existing Salem VAMC medical records and, if necessary, request appropriate X-ray testing. The radiologist will review the records and/or test results on a case-by-case basis and clear (or not) the veteran for participation in research fMRI.

The MRI scanning provided is for research data only and scans will not be used for medical or diagnostic purposes. In the rare event that an obvious abnormality is evident on a scanning image, the research team will alert Dr. Casas or Dr. Chiu. The participant will be informed of the abnormality in the scan and will be encouraged to seek consultation with their primary care provider in order to determine an appropriate course of action. Subjects also will be alerted in the informed consent that the FBRI is not a medical facility and emergency medical intervention is not available on site (all research staff are trained as CPR/First Aid responders). Please refer to attached protocol for medical emergencies at the FBRI.

During the CAPS psychiatric interview, while subjects are asked to talk about their traumatic experiences, there is a risk that detailing the event may bring up strong memories, which may in turn evoke some anxiety and distress in the subject. If that should happen, subjects will be assured that they are in a safe environment and will be given options as follows: slow down the pace of the interview or take a break. Based on our prior experience, such increased anxiety will be temporary and are common features of assessment efforts in all PTSD. The patient has the option to terminate the procedure if he/she feels the distress is unbearable.

During exposure therapy, there is the likelihood that patients may experience somatic and subjective distress. However, exposure sessions of 90 minutes normally are long enough for reactivity to subside. Although rare, an individual may experience flashback-like symptoms when imagining the trauma scene. If this occurs, the therapist will prompt the participant to be oriented to place and time. Therapists will ensure that patient distress level has subsided before the patient leaves the treatment session.

Additionally, scents will be used with the virtual reality system in exposure therapy when determined by the individual therapist to be appropriate to treatment. These scents help to provide the immersive experience necessary for the most accurate representation of the veterans' traumatic event. There are no known risks to being exposed to the scents, but the patients will be informed that they may opt out of using them at any point in their sessions.

As with any research, there is always a chance that confidentiality of the collected information may be breached. To protect participant confidentiality as much as possible, computer and paper records containing information that could be used to identify subjects individually will be stored

only on secure high-encryption servers and in locked file cabinets behind locked doors that are accessible only by authorized research staff.

At post-treatment, participants in either group who did not respond to treatment (i.e., meet non-responder criteria) will be offered clinical treatment through an outpatient clinic, other appropriate VAMC mental health clinic or non-VA health facilities in the Roanoke area. Patients whose clinical status deteriorates during the course of treatment to the extent that additional intervention is warranted will be removed from the protocol and offered appropriate clinical services. Post-treatment care recommendations and/or referrals will be provided and managed by clinical unit staff following VA clinical regulations.

Benefits: A benefit from participating in the study may be a reduction in general anxiety, intrusive symptoms, physiological reactivity, and improved interpersonal functioning. Furthermore, this research may help identify the efficacy of one treatment compared to another or identify unique characteristics that make one treatment more efficacious for certain participants.