COVER PAGE FOR PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official Study Title: Network Dysregulation Among Individuals with Co-Morbid Tinnitus and PTSD

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HUMAN SUBJECTS RESEARCH PROTOCOL

1. PROTOCOL TITLE: Network Dysregulation Among Individuals with Co-Morbid Tinnitus and PTSD

2. ABSTRACT

Tinnitus and posttraumatic stress disorder (PTSD) are two of the most common combat-related disorders. Although the defining symptoms of tinnitus (an illusory auditory percept) and PTSD (a trauma-related disorder) are clearly different, they are highly comorbid. Neurobiologically, each disorder has been characterized as functional network dysregulations, applying functional co-variance (FCov) metrics to resting-state functional magnetic resonance imaging (rs-fMRI). In PTSD, network abnormalities have been reported in the attention, limbic and default-mode networks. In tinnitus, the same networks have been reported as abnormal, with the addition of the auditory network. Given the hypothesized shared neurobiological resting state networks between tinnitus and PTSD, it is anticipated that treatment of PTSD will also help alleviate tinnitus distress.

The purpose of this study is to characterize tinnitus and PTSD symptomatically, neurobiologically, and causally, applying causal modeling to psychometric and neurofunctional data. We will enroll 30 individuals with both tinnitus and PTSD. Participants will be asked to complete baseline assessments of subjective tinnitus distress, PTSD, depression, and resting-state fMRI at baseline. Individuals with comorbid tinnitus and PTSD who are eligible for the study will receive Cognitive Processing Therapy (CPT) over a 6- to 15-week period and a mid-treatment resting-state fMRI (after Session 6 of CPT and before Session 7 of CPT). CPT is a trauma-focused treatment for PTSD that guides individuals on how to recognize and challenge thoughts that are erroneous and dysfunctional. One-month follow-up assessments of tinnitus-related distress, PTSD, depression, and anxiety will be conducted, along with resting-state fMRI.

3. OBJECTIVES/SPECIFIC AIMS/RESEARCH QUESTIONS

Objective:
The primary objective of this study is to evaluate the overlap between tinnitus-related distress and symptoms of PTSD, identify functional covariance among resting-state networks among individuals with tinnitus and PTSD, and determine psychometric and neurobiological changes among participants who receive Cognitive Processing Therapy (CPT for PTSD).

Aim 1: To identify the cognitive, behavioral, and emotional symptoms that are both shared and unique to PTSD and tinnitus-related distress.

Hypothesis 1: There will be significant overlap between tinnitus distress and PTSD symptoms, as measured by the Clinician Administered PTSD Scale for DSM-5 (CAPS-5), the PTSD Checklist for DSM-5 (PCL-5), the Tinnitus Functional

Index (TFI), and Tinnitus Acceptance Questionnaire (TAQ). Findings will help clinicians' understanding of the distinct ways in which each disorder contributes to functional impairment. Results will substantially improve clinicians' ability to conceptualize patients with comorbid tinnitus and PTSD.

Aim 2: To identify the functional covariance among resting-state networks, including the limbic, attentional, auditory, and default-mode networks associated with tinnitus and PTSD. Resting state fMRI techniques will be conducted among individuals with comorbid PTSD and tinnitus.

Hypothesis 2: There will be similar neurological activity associated with PTSD and tinnitus as measured by resting state fMRI. Down-regulation and up-regulation of neurobiological connectivity of the networks will be examined within the auditory, limbic, default-mode, and attentional networks. Results will provide insight concerning the neurological maintenance factors for both disorders. Study findings will be utilized to generate new and innovative therapeutic approaches that target specific brain regions to alleviate tinnitus and PTSD.

Aim 3: To determine relationships psychometrically, neurobiologically (as rs-fMRI network differences), and conjointly (between psychometrics and rs-fMRI). Longitudinal measures will determine both psychometric and neurobiological changes among participants who complete Cognitive Processing Therapy for PTSD (CPT for PTSD).

Hypothesis 3:

- Individuals with tinnitus and PTSD who received Cognitive Processing Therapy will demonstrate significant reductions in both PTSD symptoms and tinnitus-related distress at a one-month follow-up assessment. This study will be the first to demonstrate the importance of addressing PTSD in order to target tinnitus-related distress.
- After one month of completing CPT for individuals with both PTSD and tinnitus, a decrease in neurobiological connectivity will be demonstrated between the attention network and limbic network, demonstrating the role of cognitive control in reducing psychological distress.

4. BACKGROUND AND SIGNIFICANCE.

Tinnitus and PTSD

The genesis of tinnitus and PTSD can both be potentially associated to the same psychological and acoustic traumatic event while deployed, with clinical implications concerning the recovery of both auditory and psychological disorders. Tinnitus can be conceptualized as one such conditioned stimulus, continuing to serve as a reminder of the traumatic event (Criterion B of PTSD). In a study of Cambodian refugees, significantly more participants with PTSD had tinnitus compared to participants without tinnitus (Hinton, Chhean, Pich, Hofmann, & Barlow, 2006). Tinnitus patients were significantly more likely to have PTSD compared to participants without tinnitus. In the same study, most participants with tinnitus indicated experiencing flashbacks and an overwhelming 91.7% of those flashbacks accompanied tinnitus. Second, symptoms of avoidance (Criterion C of PTSD) are also demonstrated among individuals with tinnitus. Fagelson (2007) found similarities in avoidant symptoms between veterans with both tinnitus and PTSD; and those with only tinnitus. Individuals in both groups reported similar aversions to loud warning signals and a reduction in tolerance to loud noises. Andersson and Westin (2008) explain that individuals may choose to avoid noise and seek quieter places. Third, negative alterations in mood and cognition (Criterion D of PTSD) are observed among individuals with tinnitus. Tinnitus-associated trauma recall and catastrophic cognitions significantly predicted PTSD severity, while controlling for tinnitus severity, among Cambodian refugees suffering from both tinnitus and PTSD (Hinton et al., 2006). Fourth, individuals with tinnitus demonstrate emotional reactions that overlap with hypervigilance or hyperarousal (Criterion E of PTSD). Fagelson and Smith (2016) found that individuals with tinnitus and PTSD had significantly more negative emotional responses compared to individuals with tinnitus only and those with tinnitus and other psychological problems. These emotional reactions are similar to hyperarousal symptoms (e.g., anger, irritability, nervousness). Fagelson (2007) indicated that sleep disturbance is also a symptom of hypervigilance observed in tinnitus patients (McKenna, 2000). These studies suggest the synergistic effects between the audiologic disorder and PTSD, suggesting common etiologies and symptom presentation.

Few studies have examined the neurobiological contributions of the auditory network among PTSD patients. Researchers have noticed that PTSD patients are more sensitive to auditory sounds associated with trauma than linguistic associations (van der Kolk, 1997). Paige et al. (1990) suggested that PTSD patients inhibit stimulation that could overload their

capacity for accurate discrimination, and other studies have shown cortical abnormalities of auditory processing among patients with PTSD (Lewine, 1997). Overall, it is proposed that individuals with tinnitus and PTSD 1) fail to adequately distinguish between threat and non-threat sounds, resulting in hyperarousal, hypervigilance, avoidance of activities, and abnormalities can be observed within the auditory cortex; 2) fail to accurately interpret their traumatic event and current-day events, resulting in changes in cognition and mood, feeling distant or cut off from others, lack of ability to find pleasure in activities, and reexperiencing symptoms, and decreased activation within the executive control network can be observed; 3) failure to discriminate threat versus non-threat and accurate interpretation of the traumatic event and current day events will result in an increased activation within the limbic system, resulting in an inability to regulate emotional experiences, hyperreactivity to non-threat related cues, and lack of experiencing positive emotions.

Neuroimaging studies have demonstrated that individuals with tinnitus show increased activation in brain regions also common in psychiatric conditions (Bartels et al., 2007; Landgrebe et al., 2009; Møller, 2011). Imaging studies have implicated the auditory network, limbic network, default mode network, visual network, and dorsal attention and executive control of attention networks among patients with tinnitus (Figure 4). Similar networks are observed among individuals with PTSD, including the default mode network and central executive network.

Treatment of PTSD

Cognitive Processing Therapy (CPT). CPT is a cognitive behavioral treatment for PTSD consisting of 12 one-hour sessions (Resick, Monson, & Chard, 2017; Resick & Schnicke, 1993). CPT is delivered in three phases: education, processing, and challenging. The manualized treatment focuses on challenging beliefs and assumptions related to the trauma, oneself, and the world. Randomized clinical trials conducted by Dr. Resick of our STRONG STAR Consortium and others support CPT as an effective treatment for PTSD and other comorbid conditions in a variety of civilian trauma populations. Initial randomized clinical trials using wait-list comparisons found that CPT was effective for treating PTSD in sexual abuse survivors (Resick & Schnicke, 1992; Chard, 2005) and incarcerated males (Ahrens & Rexford, 2002). A large randomized controlled trial (N=171) compared CPT, Prolonged Exposure (PE) therapy, and a minimal-attention control group (Resick, Nishith, Weaver, Astin, & Feuer, 2002). At post-treatment, 80% of the participants treated with either CPT or PE achieved remission and no longer met criteria for PTSD. These treatment gains were maintained over the 9-month posttreatment follow-up period. Furthermore, these same participants were again assessed approximately 6 years later, and about 80% of the participants in each group continued to do well and no longer met criteria for PTSD (Resick et al., 2012). Also, 89% of the patients treated with CPT improved by at least 20 points, a clinically significant improvement, on the Clinician Administered PTSD Scale (CAPS; Blake et al. 1995).

Resick and colleagues also conducted a dismantling study (N=150) comparing the full CPT protocol to a cognitive therapy only condition (CPT-C) and a condition comprised only of the written accounts of the trauma (Resick, Galovski, et al., 2008). Each condition consisted of 2 hours of therapy per week for 6 weeks, and blind assessments were conducted before treatment, 2 weeks following the last session, and 6 months following treatment. Intent-to-treat analyses indicated that patients in all three treatment conditions improved substantially on PTSD and depression. Patients also improved on other indices of adjustment such as anxiety, anger, shame, guilt, and dysfunctional cognitions. However, there were significant group differences in symptom reduction during the course of treatment whereby the CPT-C condition reported greater improvement in PTSD than the written account condition and demonstrated more rapid clinical improvement than the full CPT condition. The cognitive-only version (CPT-C) was equally effective to the full version of CPT and was perhaps more efficient. This study will use the CPT-C version of the protocol, now re-branded as CPT (Resick, Monson, & Chard, 2017).

Treatment of PTSD and Implications for Tinnitus

This study will be the first to characterize tinnitus and PTSD independently and comorbidly, before and after treatment in terms of overt cognitive, emotional, and behavioral symptom profiles and connectivity between resting-state networks. A greater understanding of the shared and unique cognitive, emotional, and behavioral symptoms between tinnitus and PTSD is the first step toward the long-term goal of recognizing the bidirectional relationship between tinnitus and PTSD. The second long-term goal is to use identify the functional covariance among resting-state networks, including the limbic, attentional, auditory, and default mode networks associated with tinnitus and PTSD by using resting-state fMRI techniques among individuals with comorbid tinnitus and PTSD. This study will be the first to identify common functional covariance among relevant resting-state networks implicated in both tinnitus and PTSD. The third long-term goal is to

determine relationships psychometrically, neurobiologically (pre-post treatment), and conjointly between psychometrics and rs-fMRI). For co-morbid PTSD/tinnitus, we will use longitudinal measures to examine changes in resting-state networks. Individuals with both tinnitus and PTSD, who participate in fMRI imaging, will receive Cognitive Processing Therapy (CPT) for PTSD and post-treatment fMRI imaging will be conducted. It is hypothesized that the attention, default-mode, and limbic resting-state networks will be altered from participants' baseline fMRI, decreasing the awareness of tinnitus sensation, and improving functional outcomes.

5. RESEARCH DESIGN

The study will use a one-way experimental design, with one level of intervention: Cognitive Processing Therapy (CPT). Participants will complete initial baseline assessments to determine eligibility, as well as resting-state fMRI scans. After completing baseline assessments and fMRI scans, participants will be scheduled 1 therapy session to discuss psychosocial history, trauma, and current functioning, which will last approximately 1 hour. Afterwards, participants will be scheduled for 12 50–minute sessions of CPT, either once or twice per week, for 6 to 15 weeks. After completing Session 6 of CPT and before Session 7 of CPT, participants will be scheduled for a mid-treatment fMRI scan. After completing CPT, participants will be scheduled for a one-month follow-up assessment, as well as a one-month follow-up fMRI scan.

Figure 1. Study Design Overview.

6. RESEARCH PLAN

6.1 Selection of Subjects

6.1.1. Subject Population. This study will consent and screen 30 male and female veterans seeking treatment for PTSD to include 10 for analysis. Subjects will be recruited from the San Antonio community.

6.1.2. Source of Research Material. All measures are being administered for research purposes. For a complete list of measures, see Section 6.2.

6.1.3. Inclusion and Exclusion Criteria.

Inclusion Criteria

- Adult male and female military Veterans (age 18-60) who deployed in support of combat operations post-9/11 seeking behavioral health treatment for PTSD and/or tinnitus
- Diagnosis of PTSD determined by the Clinician-Administered PTSD Scale - Interview – Version 5 (CAPS-5)
- Ability to speak and read English
- Meets criteria for tinnitus and considers their tinnitus bothersome, as defined by a score on the Tinnitus Functional Index of 32 or greater

Exclusion Criteria

- Currently receiving evidence based treatment for PTSD
- Current suicidal ideation severe enough to warrant immediate attention (as determined by the Depressive Symptoms Index- Suicidality Subscale and corroborated by a clinical risk assessment by a credentialed provider
- Psychiatric hospitalization in the last 12 months
- Current and severe alcohol use warranting immediate intervention based on clinical judgment
- Current manic episode or psychotic symptoms requiring immediate stabilization or hospitalization (as determined by the manic and psychosis modules of the MINI)
- Evidence of a moderate or severe traumatic brain injury (as determined by the inability to comprehend the baseline screening questionnaires)
- Neurobiological disorders
- Meniere's disease, temporomandibular joint disorders
- History of seizures
- History of penetrating head trauma or neurosurgery
- Metal objects implanted in the head, ferrous metal filings in the eye
- Inflammation of the brain
- Cardiac pacemaker
- Implanted medical pump or cardiac lines
- Heart disease
- Currently taking certain types of medication for depression or seizures (tricyclic antidepressants or neuroleptics which lower seizure threshold)

6.1.4. Description of the Recruitment and Prescreening Process.

The study will be conducted in collaboration with the STRONG STAR Multidisciplinary PTSD Research Consortium. Primarily potential participants will self-refer to the study. General announcements and flyers will be posted on public media and at various community sites that will allow self-referral of Veterans. Potential participants may also self-refer in response to recruitment information on the STRONG STAR website. Potential participants may contact STRONG STAR if they feel that they are eligible. In addition to self-referral recruitment study staff will work closely with staff at hospital clinics (Mental Health Clinics, Substance Abuse Treatment Clinics, Primary Care Clinics, Audiology Clinics) and Veteran advocacy groups, which have been found to be reliable and productive sources of participants. Referring providers and staff can give their patients contact information for the study staff so that interested individuals may contact STRONG STAR directly. Providers can also obtain consent to contact from interested individuals so that study staff can contact them directly about study participation. In addition, there may be events where information about STRONG STAR studies

is provided and those interested may fill out a "consent to contact" form indicating that they would like a member of the research team to contact them at a later date to learn more about the study and schedule or complete pre-screening. Under an IRB approved HIPAA Waiver of Authorization, we will also review the STRONG STAR records of previous STRONG STAR and CAP study participants who met criteria for PTSD and indicated they suffered from tinnitus. Protected health information (PHI) from baseline assessments, such as scores on the CAPS-5 and Tinnitus Functional Index, will be used to determine appropriateness for the study. A member of the research team will contact by telephone individuals who appear to be appropriate for the study. Potential participants who are interested in the study will complete a pre-screening questionnaire over the phone.

Under an IRB approved HIPAA Waiver of Authorization, Alteration of Informed Consent, and Waiver of Documentation of Informed Consent, study personnel will conduct a brief telephone pre-screening where the basic study inclusion and exclusion criteria will be reviewed to help the individual determine if he or she meets the study criteria or has obvious exclusions from the study protocol so as to prevent individuals from making unnecessary travel for consent and more in-depth screening (see Appendix C). This information will be entered into a secure database as a phone call to a potential participant or a phone call from a potential participant: name, phone number, name of study the caller is interested in, referral date, referral source, potential eligibility status, reason if not eligible, and verbal permission to contact the caller in the future for other studies. We will also record the date and time of the call, outcome of the call, and any notes. Subjects who present at the Northwest Center will also be shown a video that explains the step-by-step MRI procedures to ensure that they are comfortable with scanning (Appendix D is the video to be shown, minutes 2:22 to 3:39). Appendix E is the script of this segment of the video. Subjects who agree to study participation will sign a consent document before any further screening will take place. Any individually identifiable information and Protected Health Information (PHI) collected on individuals who do not consent to participation will not become part of the research data. If participants agree to participate in the research, the identifiable data collected will become part of the participants' research records and will be stored according to the research confidentiality plan.

Veterans who phone screen out from other IRB-approved STRONG STAR protocols will be offered the opportunity to be phone screened for participation in this study. If interested, a member of the research team will review eligibility with these potential participants (e.g., pre-screen) over the phone. If the person believes they may qualify for the study, the participant will be scheduled for an appointment in which consent will be obtained, and if authorized, the baseline assessment will be completed. If not interested or Veterans who phone screen out from this study, Veterans will be offered the opportunity to be phone screened for participation in other IRB-approved STRONG STAR protocols.

6.1.5. Consent Process.
Potential participants will have the study explained to them in a safe and private location in person. The potential participant will be given a copy of the informed consent document (ICD) to read. The research team member obtaining informed consent will then engage the potential participant in an interactive explanation of the study guided by the ICD. After the subject has read the ICD, he or she will be given the opportunity to consider participation and discuss the research with family and friends. The Research Team will be available to answer any questions about the research. Once the potential participant has reached a decision, the advising staff member will review the risks and benefits of study participation and ensure the subject has an understanding of the material discussed, and the risks and benefits of their potential involvement in the study. The advising staff member will have the participant sign the consent form. A copy of the signed ICD will be given to the subject.

6.1.6. Subject Screening Procedures.
Following consent, screening and baseline assessment will take place to determine participant eligibility. The entire screening process will take approximately 3 hours. This will include the completion of the questionnaires and interviews outlined in the table in Section 6.2 below. For individuals not meeting study inclusion criteria, the Study Staff will assist coordinating appropriate care outside of the study.

6.1.7. Compensation for participation.
Participants will be compensated $75 for each neuroimaging scan: once prior to enrolling in Cognitive Processing Therapy, once at mid-treatment (after Session 6 and before Session 7), and once at the one-month follow-up after

receiving Cognitive Processing Therapy. Payment will be provided via a rechargeable MasterCard® ClinCard. The MasterCard® ClinCard is a debit card issued to the study participant. Funds are loaded onto card through the ClinCard website at www.clincard.com. Only authorized users will be able to access the ClinCard website to add funds with a username and password. The ClinCard funds will be available to recipients within 1 business day and can be used as the participant chooses. The participant will be notified that their name, address and date of birth will be shared with a third-party (ClinCard) solely for the purposes of payment processing. This information will only be used for the administration of the payment and will be kept strictly confidential.

6.1.8. Treatment Procedures.

This study will examine the effectiveness of Cognitive Processing Therapy (CPT) for the alleviation of PTSD and tinnitus-related distress among individuals with co-morbid PTSD and tinnitus.

Cognitive Processing Therapy (CPT). Prior to engaging in therapy, one session will be devoted to gathering information regarding psychosocial history, trauma, and current functioning. During the first session, a brief explanation of the connection between tinnitus and PTSD will be provided for the participants, to increase motivation and understanding of the treatment (Appendix F). The following sessions will follow the standard outpatient CPT protocol. The standard outpatient CPT (Resick, Monson, & Chard, 2017) consists of 12 one-hour sessions conducted over a 6- to 12-week period (Resick, Monson, & Chard, 2008). An additional 3 weeks will be provided in case of participant and therapist vacation and/or sick days. Participants will be considered treatment completers if they attended at least 75% of the full 12-session protocol (9 sessions). The three phases of CPT include psychoeducation, processing, and challenging beliefs and assumptions related to the trauma, oneself, and the world. CPT begins with an impact statement in which the patient describes why he or she thinks the index (worst trauma) happened, the impact of the trauma on his or her perspective of self, others, and the world. The impact statement helps to identify maladaptive cognitions about the trauma, such as “it’s all my fault” and “I can’t trust anyone.” These cognitions can emerge when a traumatic experience does not make sense in the context of previous beliefs. Throughout therapy, problematic cognitions are identified and challenged through Socratic questioning until more accurate beliefs about self, others, and the world replace any distorted cognitions. The last five sessions of CPT focus on cognitions related to specific topics that are often particularly problematic in PTSD, including safety, trust, power, esteem, and intimacy. CPT is based on cognitive theory in which traumatic events are inconsistent with prior positive beliefs or seemingly confirm negative beliefs. Because people tend to hold just world beliefs, they have difficulty reconciling events that appear to be unfair or random. People also tend to blame themselves for events or try to mentally “undo” the event and feel guilt, shame or anger, rather than the natural emotions that may have emanated directly from the event (sadness/grief, fear, horror) (Resick, Galovski, et al., 2008). All study participants will receive treatment with CPT, as it is typically conducted in the VA or another clinic, face-to-face. The patient will be seen either once or twice a week in the clinic office and the therapist will follow the protocol as specified in the manual. The patient will be given assignments that will be placed into a patient binder for them to keep. However, the therapist will also keep a folder with a copy of the stuck point log and extra copies of worksheets in case the patient forgets to bring the binder to the session.

Training, Certification, and Supervision of CPT Therapists

A detailed CPT training, certification, and supervision process has been developed to ensure that CPT is delivered according to protocol and with the highest levels of quality and fidelity. The Principal Investigator (John Moring, PhD) is a licensed clinical psychologist with extensive training and consultation provided by one of the developers of CPT, Dr. Patricia Resick. Dr. Resick, Consultant on this research study, will provide consultation on an as-needed basis.

Treatment Adherence and Competence. The fidelity to the treatment will be closely monitored to ensure that the therapy is being delivered true to the protocol. Treatment adherence and competence will be determined by independent raters who are not otherwise involved in the project. The raters will be affiliated STRONG STAR investigators who have served on prior CPT studies as adherence and competence raters. In order to ensure that the CPT treatment is administered in accordance with the manual, all sessions in the study will be audio recorded for fidelity rating. Audio recordings will be uploaded onto the secure STRONG STAR server so they can be reviewed remotely. The raters will determine adherence to the CPT therapies and competence in delivering the therapies. Five percent of all audiotapes for listening and determination of inter-rater reliabilities (kappas).

389 **6.2. Study Procedures**.
390

Study Procedures	BL Week 0	fMRI Scan Week 0	Prior to Tx	CPT Sessions 1, 3, 5, 7, 9, 11	CPT Sessions 2, 4, 6, 8, 10, 12	fMRI Scan Mid-Treatment	FU Assessment (1-Month Post Tx)	FU fMRI Scan (1-Month Post Tx)
Informed Consent	X							
1. Demographics and Military Service Characteristics Form	X							
2. Deployment Risk and Resilience Inventory (DRRI-2) Subscales: -Combat Experience –Postbattle Experiences	X							
3. MRI Participant Information and Screening Questionnaire	X						X	
4. Life Events Checklist-5 (LEC-5)	X						X	
5. Trauma Related Guilt Inventory (TRGI)	X				X		X	
6. Depressive Symptom Index Suicide Subscale (DSI-SS)	X						X	
7. Generalized Anxiety Disorder-7 (GAD-7)	X						X	
8. Selection of Index Event for CAPS-5	X							
9. Clinician-Administered PTSD Scale – 5 (CAPS-5)	X						X	
10. PTSD Check List – DSM-5 (PCL-5)	X				X		X	
11. Self-Injurious Thoughts and Behaviors Interview- Short Form (SITBI-Short Form)	X						X	
12. Health Questionnaire	X						X	
13. History of Head Injuries	X						X	
14. Veterans Rand 12-Item Health Survey (VR-12)	X						X	
15. Insomnia Severity Index (ISI)	X						X	
16. PROMIS Sleep-Related Impairment and Sleep Disturbance	X						X	
17. Snoring, Tired, Observed, Blood Pressure (STOP) Sleep Apnea Screen	X						X	
18. Patient Health Questionnaire – 9 (PHQ-9)	X			X			X	
19. Fagerstrom Test for Nicotine Dependence (FTND)	X						X	
20. Fagerstrom Test for Nicotine Dependence-Smokeless Tobacco (FTND-ST)	X						X	

21. Alcohol Use Disorders Identification Test (AUDIT)	X						X	
22. Quick Drinking Screen (QDS)	X						X	
23. Mini-International Neuropsychiatric Interview (MINI)- Manic and Psychosis modules	X							
24. Tinnitus Functional Index (TFI)	X			X			X	
25. Tinnitus Acceptance Questionnaire (TAQ)	X						X	
26. Brief Inventory of Psychosocial Functioning (BIPF)	X						X	
27. Homework Compliance				X	X			
28. fMRI scan		X				X		X
29. Trauma Interview			X					

6.3.2 Data Collection.

6.3.2.1 Instrumentation:
See the table at Section 6.2 above for a summary of the assessments and timing of administration. A description of each of the assessments can be found at the end of this protocol. Assessments will be administered in person whenever possible. However, in order to accommodate participant schedules and/or instances in which a participant does not reside in the local area at the time of a follow up assessment, we may collect full or partial assessments in person or via phone. Reasonable efforts will be made to collect all data as described in this protocol, but we expect some participants may not be able to complete part or all of any given follow up assessment.

6.3.2.2. Resting state *f*MRI.
Participants who are eligible to continue in the study after consent and screening will undergo a function magnetic resonance imaging (MRI) session at the Research Imaging Institute (RII) at the University of Texas Health Science Center at San Antonio. Participants who cannot tolerate the MRI procedure will be withdrawn from the study. Participants will receive a mid-treatment scan (after Session 6 of CPT and before Session 7 of CPT), and a follow-up fMRI scan one month after completing therapy. Each MRI scan may take up to 2 hours.

6.3.2.3 Data Storage and Access:
Data will be coded using an assigned number. Paper research data will be kept in locked file cabinets in locked offices at the University of Texas Health Science Center San Antonio (UTHSCSA) STRONG STAR offices. Data collected will be entered into a spreadsheet located on a secure STRONG STAR server. Audio-recordings will be uploaded to a secure STRONG STAR server over an encrypted network connection. Neuroimaging data will be kept on secure networks at the Research Imaging Institute. Every member of the Research Team will be trained and monitored about how to handle and protect both medical and research records. Furthermore, the Research Team strictly controls access to study data using policies and procedures developed specifically for the STRONG STAR Research Consortium.

Every member of the Research Team will be trained and monitored about how to handle and protect research records. Furthermore, the Research Team strictly controls access to study data.

6.4 Statistical Consideration

6.4.1 Sample Size Estimation.
The recruited sample size will be 30 participants. Based on work by Salinas and Szabo (2017), 10 participants will provide adequate power to detect differences in resting-state networks, from pre-, mid- and to posttreatment fMRI scans. In their

paper, they examined 14 baboons, pre- and posttreatment injection of valproic acid, at three different time points, with adequate power.

Estimate Required Sample Size	**10**
Estimate Participant Screen Out	**18 (~60%)**
Estimate Participant Withdrawal	**2 (~7%)**
Total Enrollment Requirement	**30**

6.4.2 Primary (i.e., primary outcome variables) and secondary endpoints.

Primary outcomes include changes in scores on measures of PTSD (CAPS-5 and PCL-5) and tinnitus-related distress (TFI and TAQ). The additional primary outcome is changes in functional activity within resting-state networks, provided by fMRI scans.

Secondary outcome variables include changes in scores on measures of depression and suicide (DSSI-SS; PHQ-9), anxiety (GAD-7), sleep impairment (PROMIS; ISS; STOP), general health and functioning (VR-12; BIPF), and alcohol and substance use (FTND; FTND-ST; AUDIT).

6.4.3 Hypotheses and Specific Data Analysis Plans.

Hypothesis 1: There will be significant overlap between tinnitus distress and PTSD symptoms, as measured by the Clinician Administered PTSD Scale for DSM-5 (CAPS-5), the PTSD Checklist for DSM-5 (PCL-5), the Tinnitus Functional Index (TFI), and Tinnitus Acceptance Questionnaire (TAQ). Findings will help clinicians' understanding of the distinct ways in which each disorder contributes to functional impairment. Results will substantially improve clinicians' ability to conceptualize patients with comorbid tinnitus and PTSD.

Analysis plan: Non-inferential statistics will be calculated to include central tendencies, standard deviations, and alpha coefficients. Unusual distributions, missing data, or outliers will be identified. PTSD symptom cluster severity (intrusions, avoidance, negative alterations in mood and cognition, and hyperarousal) will be calculated using the data gathered from the CAPS-5. Tinnitus domains of distress will be calculated using the data gathered from the Tinnitus Functional Index. Pearson product-moment correlation coefficient analyses will be used to examine the overlap between tinnitus and PTSD.

Hypothesis 2: There will be similar neurological activity associated with PTSD and tinnitus as measured by resting state fMRI. Down-regulation and up-regulation of neurobiological connectivity of the networks will be examined within the auditory, limbic, default-mode, and attentional networks. Results will provide insight concerning the neurological maintenance factors for both disorders. Study findings will be utilized to generate new and innovative therapeutic approaches that target specific brain regions to alleviate tinnitus and PTSD.

Analysis plan: An inter-regional connectivity mapping using an extended time-series (typically 200-400 whole-brain volumes acquired over 8-15 minutes) of BOLD fMRI images acquired in an unstimulated state (Biswal et al., 1995; Xiong et al., 1999) will be utilized for Aim 2. Inter-connected regions show temporally correlated variations, allowing connectivity to be detected and quantified. Resting-state networks (RSNs) have been used to map scores of functional systems. They are now viewed as reflecting the intrinsic architecture of the brain (Smith et al. 2009). Resting-state connectivity analysis of the auditory system in normal subjects demonstrated highly coherent within-system connectivity, as well as strong projections to the frontal limbic circuitry (Hunter et al., 2006). Resting-state connectivity analyses will be used to characterize tinnitus-related network abnormalities.

Hypothesis 3:

- Individuals with tinnitus and PTSD who received Cognitive Processing Therapy will demonstrate significant reductions in both PTSD symptoms and tinnitus-related distress at a one-month follow-up assessment, AND
- After one month of completing CPT for individuals with both PTSD and tinnitus, a decrease in neurobiological connectivity will be demonstrated between the attention network and limbic network, demonstrating the role of cognitive control in reducing psychological distress.

Analysis plan: Post-treatment outcome data will be compared to participants' baseline measures of tinnitus-related distress and PTSD. Data will be analyzed using a general linear mixed (GLM) model with baseline scores of tinnitus-related distress used as a covariate. The analyses will demonstrate whether individuals who received CPT experienced a reduction in tinnitus-related distress and PTSD symptoms.

An inter-regional connectivity mapping using an extended time-series (typically 200-400 whole-brain volumes acquired over 8-15 minutes) of BOLD fMRI images acquired in an unstimulated state will be utilized for Aim 3. Resting-state connectivity analyses will be used to better characterize tinnitus-related network abnormalities using Independent Components Analysis, using analysis of variance (ANOVA) comparing Baseline versus Posttreatment factors, while regressing out demographic variables. The mid-treatment scan will be used to infer causal effects of Cognitive Processing Therapy by demonstrating the temporal changes in resting-state networks.

Missing data. If missing data can be assumed to be missing at random, likelihood-based mixed model analysis will provide valid inferences using data from all cases with any outcome data. The impact of attrition on analyses will be addressed by comparing those who are available for analysis at each assessment with those who are not using appropriate data from prior assessments.

6.7 Confidentiality. All in-person therapy sessions and interview assessments will be delivered in private offices at the STRONG STAR Clinic at the UTHSCSA. Data will be stored by an assigned participant code number. Digital audio recordings of assessments and CPT sessions will be labeled with the participant's study id number and uploaded onto the secure STRONG STAR server. Encrypted email will be used to securely send recordings to research experts who are part of the research team for review of fidelity. Every member of the Research Team will be trained and monitored about how to handle and protect both medical and research records. Furthermore, the Research Team strictly controls access to study data.

6.7.1 Certificate of Confidentiality.
We are not seeking a Certificate of Confidentiality.

6.7.2. Data Protection. Data will be coded using an assigned number. Assessments and data collected during the treatment sessions will be stored in a locked cabinet at the STRONG STAR Clinic at the UTHSCSA. Digital audio recordings of assessments and CPT sessions will be labeled with the participant's study id number and uploaded onto the secure STRONG STAR server. All UTHSCSA STRONG STAR network connectivity is segmented with Access Control Lists and is not accessible to any other UTHSCSA network segments. STRONG STAR data server is physically located at the Advanced Data Center (ADC) has 24x7 onsite security, card key, biometric access controls and video surveillance. University of Texas Health Science Center at San Antonio (UTHSCSA) ADC facility also maintains Gen 2 firewall devices to protect and prohibit any unauthorized access to UTHSCSA data. All UTHSCSA network devices are monitored by state of the art monitoring applications that include configuration audit, management, and availability 24x7.

7.0 RISKS/BENEFITS ASSESSMENT

7.1 Risks.

Risks and Side Effects related to Cognitive Processing Therapy
Likely, but not Serious, expected to occur in more than 20 out of 100 participants:

- Emotional distress or experiencing an initial increase of PTSD symptoms due to the discussion of traumatic events. However, in past research conducted by STRONG STAR investigators using CPT-C, there have been no serious adverse events or related difficulties with emotionally upset participants due to the treatments.

Risks and Side Effects related to the Assessment of Tinnitus

Rare, but not Serious, expected to occur in less than 5 out of 100 participants:

- Emotional distress due to tinnitus or more attention toward tinnitus sensation may occur; however, since tinnitus is a chronic and stable condition, it is unlikely that a change will occur because of the assessment procedures

Risks and Side Effects related to the Resting-State fMRI

Rare, but not Serious, expected to occur in less than 5 out of 100 participants:

- Confinement claustrophobia (fear of tight spaces). During the MRI scan, participants will be asked to remain perfectly still. The MRI can cause individuals to feel claustrophobic (fear of tight spaces). However, the incidence of claustrophobia with the MRI is low (approximately 1 per 150 persons).

Rare and Serious, expected to occur in less than 5 out of 100 participants:

- Foreign bodies which may interact with the magnetic field of the MRI can have risk for persons with foreign bodies implanted in their body. Cardiac pacemakers and cochlear implants may cease to function and can be permanently damaged by the MRI. Surgical clips on aneurysms and intestines may be moved by the magnetic field. Ferrous metal filings in the eye (e.g., in machinists) can be moved by the magnetic field. Foreign body risk is minimized by including only volunteers with no known foreign bodies and no exposure to circumstances, which might predispose to foreign bodies (e.g., metal machine workers). Before any MRI you receive, we will ask you about any metal objects that may be in your body in order to ensure your safety.

Risks of PTSD Diagnosis regardless of Treatment

One of the risks of PTSD both in and out of treatment is attempted suicide, which can result in death.

Safeguards for Protecting Participants: During the early sessions of treatment, participants will be provided immediate coping tools and techniques used to manage distressing emotions by the study therapist. Distress experienced by participants is expected to be temporary. Any indication that the participant is considering suicide will be handled using processes developed by military and civilian Consultants for the STRONG STAR Consortium studies. Trained clinicians and evaluators will assess history of suicide and current suicidal ideation using the following standardized measures: Self-Injurious Thoughts and Behaviors Interview- Short Form (SITBI- Short Form) and the Patient Health Questionnaire-9 (PHQ-9). For participants identified as having low to moderate risk for suicide based on the assessment results, the patient will be maintained on protocol and additional risk management procedures will be implemented within the context of the study treatment. For participants identified as being at high risk for suicide based on the assessment results, disenrollment will be considered if it is unlikely that standard treatment plus additional risk management procedures will maintain safety. High risk participants who are disenrolled from the study will be referred for more intensive treatment (outpatient or inpatient).

A STRONG STAR Data Safety and Monitoring Plan (DSMP) has been developed in accordance with the National Institutes of Health (NIH) Office of Human Research Protection (OHRP) to assure the appropriate clinical safety and adverse event monitoring of study subjects participating in STRONG STAR studies.

7.2 Potential Benefits.

Potential benefits of participation in this study may include a reduction in PTSD symptoms and tinnitus-related distress over the course of therapy. Our primary goal is to treat participants to the point of symptom reduction below the level of diagnostic criteria for PTSD. In addition, the knowledge gained from this study will serve to inform the most effective early interventions for the treatment of co-morbid tinnitus and PTSD in Veterans.

7.3 Alternatives: Other treatments for PTSD that are available include the following:

- Various forms of psychotherapy (talk therapy) including CPT for PTSD.
- Various forms of psychotherapy (talk therapy) including Acceptance and Commitment Therapy for tinnitus
- Drug treatments for PTSD
- There may be other research studies involving experimental treatments that could be helpful in treating PTSD and/or tinnitus

Not participating in this study is an option.

8.0 ADVERSE EVENTS, UNANTICIPATED PROBLEMS, AND DEVIATIONS

8.1 Adverse Events will be assessed and monitored according to the established STRONG STAR SOP and the IRB of record's policies and procedures.

8.2 Reporting Adverse Events, Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), and Deviations to the Office of the IRB.

All adverse events, unanticipated problems involving risk to subjects or others, and deviations will be reported to the Institutional Review Board (IRB) in accordance with current IRB policy. UPIRSOs and recurrent non-compliance with study procedures will be reported promptly to the IRB. All adverse events that do not meet the UPIRSO criteria and deviations that are not non-compliance will be summarized at Continuing Review per the IRB of record's policy.

9.0 WITHDRAWAL FROM STUDY PARTICIPATION.

Participation in the study may be discontinued by the principal investigator if continued participation is considered a danger to a participant's welfare. Reasons for discontinuation include: 1) a serious adverse event such that continued participation would be a danger to the participant; 2) clinical worsening for any reason that is deemed to necessitate non-study psychological or psychiatric treatment; 3) exacerbation of PTSD, anxiety, or depressive symptoms that the participant cannot tolerate; 4) inability to tolerate the MRI procedure; or 5) discontinuation would be in the participant's best interest.

Participants who are discontinued from the study for any reason will be scheduled for a final evaluation within one week and given appropriate treatment referrals. If participants are discontinued due to a serious adverse event, they will continue to be followed clinically by the therapist and/or member of the research staff until the adverse event is resolved or becomes stable. If participants are discontinued for a medical or psychiatric reason, they will be given the opportunity to either complete the balance of their CPT sessions or to receive a full course of CPT after the condition has resolved or stabilized and the endpoint assessment has been completed. The reason the participants are discontinued from the study and any referrals made will be documented. Participants will be told they will be contacted for follow-up assessments (excluding fMRI scans) whether or not they complete the treatment trial.

10.0 REFERENCES.

Ahrens, J., & Rexford, L. (2002). Cognitive processing therapy for incarcerated adolescents with PTSD.Journal Of Aggression, Maltreatment & Trauma, 6(1), 201-216.

Andersson, G., & Westin, V. (2008). Understanding tinnitus distress: Introducing the concepts of moderators and mediators. *International Journal of Audiology, 47*(Suppl 2), S106-S111.

Bartels, H., Staal, M.J., & Albers, F.W.J. (2007). Tinnitus and neural plasticity of the brain. *Otological Neurotology, 28*, 178-184.

Biswal, B., Yetkin, F.Z., Haughton, V.M., & Hyde, J.S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magnetic Resonance Medicine, 34, 537-541.

Chard, K. M. (2005). An evaluation of cognitive processing therapy for the treatment of posttraumatic stress disorder related to childhood sexual abuse. Journal of Consulting and Clinical Psychology, 73, 965–971.

Fagelson, M.A. (2007). The association between tinnitus and posttraumatic stress disorder. *American Journal of Audiology, 16*, 107-117.

Fagelson, M.A., & Smith, S.L. (2016). Tinnitus self-efficacy and other tinnitus self-report variables in patients with and without post-traumatic stress disorder. *Ear and Hearing*. Advance online publication.

Hinton, D.E., Chhean, D., Pich, V., et al. (2006). Tinnitus among Cambodian refugees: Relationship to PTSD severity. *Journal of Traumatic Stress, 19*, 541-546.

Hunter, M.D., Eickhoff, S.B., Miller, T.W.R., et al. (2006). Neural activity in speech-sensitive auditory cortex during silence. *PNAS, 103*, 189-194.

Landgrebe, M., Langguth, B., Rosengarth, K., et al. (2009). Structural brain changes in tinnitus: Grey matter decrease in auditory and non-auditory brain areas. *Neuroimage, 46,* 213-218.

Lewine, J.D., Canive, J.M., Orrison, W.W., et al. (1997). Electrophysiological abnormalities in PTSD. Annals of the New York Academy of Sciences, 821, 508-511.
McKenna L (2000). Tinnitus and insomnia. In R. Tyler (Ed.), Tinnitus handbook (pp. 59-84). San Diego, CA: Singular.
Møller, A.R. (2011). The role of neural plasticity in tinnitus. In A.R. Møller, B. Langguth, D. De Ridder, & T. Kleinjung (Eds.), *Textbook of tinnitus* (pp. 99-102). New York, NY: Springer Science.
Paige, S., Reid, G., Allen, M. et al. (1990). Psychophysiological correlates of posttraumatic stress disorder in Vietnam veterans. *Biological Psychiatry, 27*, 419-430.
Resick, P.A., Galovski, T.A., Uhlmansiek, M. O., Scher, C.D., Clum, G. A., & Young-Xu, Y. (2008). A randomized clinical trial to dismantle components of cognitive processing therapy for posttraumatic stress disorder in female victims of interpersonal violence. Journal of Consulting and Clinical Psychology, 76, 243–258.
Resick, P.A., Monson, C.M., & Chard, K.M. (2017). Cognitive Processing Therapy: A comprehensive manual. New York, NY: The Guilford Press.
Resick, P. A., Nishith, P., Weaver, T. L., Astin, M. C., & Feuer, C. A. (2002). A comparison of cognitive processing therapy, prolonged exposure and a waiting condition for the treatment of posttraumatic stress disorder in female rape victims. Journal of Consulting and Clinical Psychology, 70, 867–879.
Resick, P. A., & Schnicke, M. K. (1992). Cognitive processing therapy for sexual assault victims. Journal of Consulting and Clinical Psychology, 60(5), 748–756.
Resick, P. A., Williams, L. F., Suvak, M. K., Monson, C. M., & Gradus, J. L. (2012). Long-term outcomes of cognitive–behavioral treatments for posttraumatic stress disorder among female rape survivors. Journal of Consulting and Clinical Psychology, 80, 201–210.
Smith, S.M., Fox, P.T., Miller, K.L. et al. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences, 106*, 13040-13045.
Van der Kolk, B.A., Pelcovitz, D., Roth, S. et al. (1996). Dissociation, somatization, and affect dysregulation: The complexity of adaptation of trauma. *American Journal of Psychiatry, 153*, 83-93.
Xiong, J., Gao, J.H., Lancaster, J.L., Fox, P.T. (1999). Interregional connectivity to primary motor cortex revealed using MRI resting state images. Human Brain Mapping, 8, 151-156.

10.1 Measurement Bibliography:

Adhikari, B., Jahanshad, N., Shukla, D., Glahn, D.C., Blangero, J., Fox, P.T., Reynolds, R.C., Cox, R.W., Fierearms, El, Veraart, J., Novikov, D.S., Nichols, T.E., Hong, L.E., Thompson, P.M., & Kochunov, P. (2018). Comparison of heritability estimates on resting state fMRI connectivity phenotypes using the ENIGMA analysis pipeline. Human Brain Mapping, 1-10. DOI: 10.1002/hbm.24331
Babor, T. F., Higgins-Biddle, J. C., Saunders, J. B. & Monteiro, M. G. (2001). *The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care, 2nd Edition.* Geneva, Switzerland: World Health Organization.
Bastien, C. H., Vallieres, A., Morin, C. M., (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Medicine, 2*(4), 297-307.
Batterham, P. J., Ftanou, M., Pirkis, J., Mackinnon, A. J., Beautrais, A., Fairweather-Schmidt, A. K., & Christensen, H. (2014, December 15). A systematic review and evaluation of measures for suicidal ideation and behaviors in population-based research. *Psychological Assessment.* Advance online publication. http://dx.doi.org/10.1037/pas0000053
Buysse, D. J., Yu, L., Moul, D. E., Germain, A., Stover, A., Dodds, N. E., Johnston, K. L., Shablesky-Cade, M. A., & Pilkonis, P. A. (2010). Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. *Sleep, 33,* 781-792.
Cameron, I. M., Crawford, J. R., Lawton, K., & Reid, I. C. (2008). Psychometric comparison of PHQ-9 and HADS for measuring depression severity in primary care. *British Journal of General Practice, 58,* 32-36.
Chung, F., Yegneswaran, B., Liao, P., Chung, S. A., Vairavanathan, S., Islam, S., Khajehdehi, A., & Shapiro, C. M. (2008). STOP questionnaire: A tool to screen patients for obstructive sleep apnea. *Anesthesiology, 108,* 812-921.
De Menses-Gaya, I. C., Zuardi, A. W., Loureiro, S. R., de Souza Crippa, J. A. (2009). Psychometric properties of the Fagerstrom Test for Nicotine Dependence. *Jornal Brasileiro de Pneumologia, 35,* 73-82.
Ebbert, J. O., Patten, C. A., & Schroeder, D. R. (2006). The Fagerstrom Test for Nicotine Dependence – Smokess Tobacco (FTND-ST). *Addictive Behaviors,31,* 1716-1721.
Ferketich, A. K., Wee, A. G., Schultz, J., & Wewers, M. E. (2007). A measure of nicotine dependence for smokeless tobacco users. *Addictive Behaviors, 9,* 1970-1975.

Gray, M. J., Litz, B. T., Hsu, J. L., Lombardo, T. W. (2004). Psychometric properties of the Life Events Checklist. *Assessment, 11*, 330-341.
Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerstrom, K. O. (1991). The Fagerstrom Test for Nicotine Dependence: A revision of the Fagerstrom Tolerance Questionnaire. *British Journal of Addiction, 86,* 1119-1127.
Henry, J.A., Stewart, B.J., Abrams, H.B., Newman, C.W., Griest, S., Martin, W.H., Myers, P.J., & Searchfield, G. (2014) Tinnitus Functional Index—Development and Clinical Application. *Audiology Today, 26*, 40-48.
Kazis, L. E., Selim, A., Rogers, W., Ren, X. S., Lee, A., & Miller, D. R. *Veterans RAND 12-Item Health Survey (VR-12): A White Paper Summary*. Unpublished manuscript. http://www.hosonline.org/surveys/hos/download/veterans_rand_12_item_health_survey_white_paper_summary.pdf
Kroenke, K., Spitzer, R. L., & Williams, J. B. W. (2001). The PHQ-9: Validity of a brief depression severity measure. *Journal of General Internal Medicine, 16,* 606-613.
Kroenke, K., Spitzer, R. L., Williams, J. B., & Lowe, B. (2010). The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: A systematic review. *General Hospital Psychiatry, 32,* 345-359.
Kubany, E. S., Haynes, S. N., Abueg, F. R., Manke, F. P., Brennan, J.M., Stahura, C. (1996). Development and validation of the Trauma-Related Guilt Inventory (TRGI). *Psychological Assessments, 8*, 423-444.
Lowe, B., Decker, O., Muller, S., Brahler, E., Schellberg, D., Herzog, W., & Herzberg, P. Y. (2008). Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. *Medical Care, 46,* 266-274.
Marx, B. P. (2013). *Development and validation of a PTSD-related impairment scale.* Retrieved from www.dtic.mil/cgi-bin/GetTRDoc?AD=ADA585414
Metalsky, G. I., & Joiner, T. E. (1997). The Hopelessness Depression Symptom Questionnaire. *Cognitive Therapy and Research, 21,* 359-384.
Morin, C.M. (1993). *Insomnia: Psychological Assessment and Management.* New York, NY: The Guilford Press.
Nock, M. K., Holmberg, E. B., Photos, V. I., & Michel, B. D. (2007). Self-Injurious Thoughts and Behaviors Interview: Development, reliability, and validity in an adolescent sample. *Psychological Assessment, 19,* 309-317.
Roy, M., Dum, M., Sobell, L. C., Sobell, M. B., Simco, E. R., Manor, H., & Palmerio, R. (2008). Comparison of the Quick Drinking Screen and the alcohol Timeline Followback with outpatient alcohol abusers. *Substance Use and Misuse, 43,* 2116-2123.
Saunders, J. B., Aasland, O. G., Babor, T. F., De La Fuente, J. R. & Grant, M. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction, 88,* 791-804.
Schwab, K. A., Baker, G., Ivins, B., Sluss-Tiller, M., Lux, W., & Warden, D. (2006). The Brief Traumatic Brain Injury Screen (BTBIS): Investigating the validity of a self-report instrument for detecting traumatic brain injury (TBI) in troops returning from deployment in Afghanistan and Iraq. [Abstract]. *Neurology, 66*(5)(Supp. 2), A235.
Schwab, K. A., Ivins, B., Cramer, G., Johnson, W., Sluss-Tiller, M., Kiley, K., Lux, W. & Warden, D. (2006). Screening for traumatic brain injury in troops returning from deployment in Afghanistan and Iraq: Initial investigation of the usefulness of a short screening tool for traumatic brain injury. *Journal of Head Trauma Rehabilitation, 22*(6), 377-389.
Sobell, L. C., Agrawal, S., Sobell, M. B., Leo, G. I., Young, L. J., Cunningham, J. A., Simco, E. R. (2003). Comparison of a Quick Drinking Screen with the Timeline Followback for individuals with alcohol problems. *Journal of Studies on Alcohol, 64,* 858-861.
Spitzer, R. L., Kroenke, K., & Williams, J. B. W. (1999). Validation and utility of a self-report version of the PRIME-MD: The PHQ primary care study. *Journal of the American Medical Association, 282*, 1737-1744.
Spitzer, R. L., Kroenke, K., Williams, J. B., & Lowe, B. (2006). A brief measure for assessing generalized anxiety disorder: The GAD-7. *Archives of Internal Medicine, 166,* 1092-1097.
Vogt, D. S., Smith, B. N., King, L. A., King, D. W., Knight, J. A., & Vasterling, J. J. (2013). Deployment Risk and Resilience Inventory-2 (DRRI-2): An updated tool for assessing psychosocial risk and resilience factors among service members and veterans. *Journal of Traumatic Stress, 26*, 710-717.
Weathers, F.W., Blake, D.D., Schnurr, P.P., Kaloupek, D.G., Marx, B.P., & Keane, T.M. (2013). *The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5).* Interview available from the National Center for PTSD at www.ptsd.va.gov.
Weathers, F. W., Blake, D. D., Schnurr, P. P., Kaloupek, D. G., Marx, B. P., & Keane, T. M. (2013). *The Life Events Checklist for DSM-5 (LEC-5).* Instrument available from the National Center for PTSD at www.ptsd.va.gov.
Weathers, F. W., Keane, T. M., & Davidson, J. R. (2001). Clinician-administered PTSD scale: A review of the first ten years of research. *Depression and Anxiety*, *13*, 132–156.

Weathers, F. W., Litz, B. T., Herman, D. S., Huska, J. A., & Keane, T. M. (1993). *The PTSD Checklist (PCL): Reliability, validity, and diagnostic utility.* Paper presented at the 9th Annual Conference of the ISTSS, San Antonio, TX.
Weathers, F. W., Litz, B. T., Keane, T. M., Palmieri, P. A., Marx, B. P., & Schnurr, P. P. (2013). *The PTSD Checklist for DSM-5 (PCL-5).* Instrument available from the National Center for PTSD at www.ptsd.va.gov.
Weise, C., Kleinstauber, M., Hesser, H., Westin, V.Z., & Andersson, G. (2013). Acceptance of tinnitus: Validation of the Tinnitus Acceptance Questionnaire. *Cognitive Behaviour Therapy, 42*, 100-115.
Westin, V., Hayes, S.C., & Andersson, G. (2008). Is it the sound or your relationship to it? The role of acceptance in predicting tinnitus impact. *Behavior Research and Therapy, 46*, 1259-1265.
Yu, L., Buysse, D. J., & Germain, A. (2012). Development of short forms from the PROMIS Sleep Disturbance and Sleep-Related Impairment item banks. *Behavioral Sleep Medicine, 10,* 6-24.

11.0 TIME REQUIRED TO COMPLETE THE RESEARCH (including data analysis). 24 months

12.0 STUDY CLOSURE PROCEDURES At the conclusion of the study (following completion of manuscripts) or termination by either the Investigators or the IRB, all data not included in the STRONG STAR Repository (UTHSCSA IRB protocol HSC20100475H) will be stripped of identifiers. De-identified (anonymized) data will be maintained indefinitely. Informed consent documents will be stored securely for a minimum of three years following completion of the research; HIPAA authorizations will be stored for a minimum of six years IAW Federal regulations. A protocol completion form will be filed with the IRB.

13.0 Funding:

This study is being funded by the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant KL2 TR002646.

14.0 Description of Assessments:

Assessments will take place at baseline and one month following treatment.

Personality & History

1. Demographics and Military Service Characteristics Form. The Demographics Form measures standard demographics (race, gender, age) and military service information (e.g., rank).

2. MRI Participant Information and Screening Questionnaire. The MRI Participant Information and Screening Questionnaire measures demographics (race, gender, age), as well as information necessary to evaluate whether an individual is able to receive an fMRI scan based on medical history (for example, neurostimulators, hearing aids, any type of coil, filter, or stent, any type of metal object).

Deployment Stress, Adversity & Trauma

3. Deployment Risk and Resilience Inventory (DRRI-2) Combat Experience.

4. Deployment Risk and Resilience Inventory (DRRI-2) Postbattle Experiences. High- and low-intensity deployment stress exposure will be assessed using scales from the DRRI-2 (Vogt, Smith, King, & King, 2012). The DRRI-2 is an update of the original DRRI (King, King, Vogt, Knight, & Samper, 2006), which was developed and tested in three separate national samples of veterans of the first Gulf War. It has been revised and tested with OEF/OIF/OND returnees (Vogt et al., 2008). The DRRI-2 provides an update of the DRRI's assessment of deployment-related factors to ensure the instrument's applicability across a variety of deployment circumstances (e.g., different eras of service) and military subgroups (e.g., men and women), as well as to validate updated measures in a contemporary Veteran cohort (Vogt, et al., 2012). High intensity stressor exposures will be assessed using the DRRI Combat Experiences and Postbattle Experiences subscales. Responses to these scales are on a 6-point Likert scale. The total score is the sum of the item scores, where higher scores signify greater exposure to combat or exposure to the consequences of combat, respectively. Both subscales have very good internal consistency (α = .90 to .92) and construct validity (Vogt et al., 2012).

5. Life Events Checklist-5 (LEC-5). The LEC-5 includes a list of 24 potentially traumatic life events commonly associated with PTSD symptoms. The instrument was designed to facilitate the diagnosis of PTSD (Weathers, Blake, Schnurr, Kaloupek, Marx, & Keane, 2013a).). In this study, the LEC-5 will also be used to identify the index event and focus of the PTSD treatment. For each potentially traumatic life event, respondents rate their experience of that event on a 5-point nominal scale (1 = happened to me, 2 = witnessed it, 3 = learned about it, 4 =part of my job, 5= not sure, and 6 = does not apply). Each nominal point will be scored separately, as either 0 (=not endorsed by participant) or 1 (=endorsed by participant).

6. Trauma Related Guilt Inventory (TRGI). The TRGI was developed to assess guilt feelings and attitudes about a specific traumatic event (Kubany, Haynes, Abueg, Manke, Brennan, Stahura, 1996). Often survivors of trauma experience guilt related to the trauma about things they did or did not do or feelings they had or did not have. A combat veteran may experience guilt about having provided first aid to some of his or her wounded colleagues but not others even though it was not possible to care for everyone. Or, an individual may experience survivor's guilt not understanding why he lived while others died. These feelings of guilt can be important in evaluating the various treatments for PTSD. The TRGI is scored into three scales (i. e., 4-item Global Guilt Scale, 6-item Distress Scale, and a 22-item Guilt Cognitions Scale) and 3 subscales (i. e., the Hindsight-Bias / Responsibility Subscale, the Wrongdoing Subscale, and the Lack of Justification Subscale). Psychometric testing has been conducted using almost 600 individuals including 357 university students, 163 women receiving counseling services in a battered women's program, and 74 Vietnam veterans. Internal consistency was high across all the testing samples. In the sample of Vietnam veterans the alpha coefficient ranged from 0.66 to 0.94. In the Vietnam veterans, the scores on the various scales and subscales were significantly correlated with the Posttraumatic CheckList – Military (PCL-M), the Mississippi Scale for Combat-Related Posttraumatic Stress Disorder, the Zung Self-Rating Depression Scale, the Guilt Inventory, and the Social Avoidance and Distress Scale with reliability coefficients ranging from 0.36 to 0.77 ($p<.05$). In a sample of 32 university students, the test-retest correlations after two days ranged from 0.74 to 0.83. An abbreviated 16-item version of the TRGI will be used in the STRONG STAR studies allowing only for the calculation of the three subscale scores. The Hindsight-Bias / Responsibility Subscale score = (sum of scores on Items 1, 5, 9, 14, 19, 23, and 26) divided by 7. The Wrongdoing Subscale score = (sum of scores on Items 3, 7, 11, 16, and 21) divided by 5. And, the Lack of Justification Subscale score = [sum of scores on Items 4 (R), 8 (R), 12 (R), and 17 (R)] divided by 4.

Psychiatric Status & History

7. Depressive Symptom Index Suicide Subscale (DSI-SS). The DSI-SS (Metalsky & Joiner, 1997) will be used to assess current suicidal ideation. The DSI-SS is a 4-item self-report measure of suicidal ideation that focuses on ideation, plans, perceived control over ideation, and impulses for suicide. It is being used as a core measure in the Military Suicide Research Consortium. Scores on each item range from 0 to 3, with higher scores reflecting greater severity of suicidal ideation. Instructions will instruct the participants to respond based on the past two weeks (for baseline and follow up visits) or the past week (for interim assessment visits). A systematic review of measures of suicidal ideation and behaviors found that the DSI-SS had evidence of excellent internal consistency and concurrent validity (Batterham et al., 2014).

8. Generalized Anxiety Disorder-7 (GAD-7). The GAD-7 (Spitzer, Kroenke, Williams, & Lowe, 2006) will be used to assess generalized anxiety symptomology. This is a 7-item measure that asks participants to rate the frequency with which they have been bothered by anxiety symptoms within the past two weeks on a scale ranging from 0 ("not at all") to 3 ("nearly every day"). Scores on all items are summed to obtain a total severity score. Scores reflect no significant anxiety symptoms (0-4), mild anxiety symptoms (5-9), moderate anxiety symptoms (10-14), and severe anxiety symptoms (>15). Respondents also indicate the degree to which their anxious symptoms have made it difficult for them to do their work, take care of things at home, or get along with other people, from "not difficult at all" to "extremely difficult." The GAD-7 has been shown to have high internal consistency (e.g., α = .89; Lowe et al., 2008) and has been shown to reliably discriminate between anxious and non-anxious diagnostic groups (Kroenke, Spitzer, Williams, & Lowe, 2010).

9. Selection of Index Event for CAPS-5. This form will be used as a supplement to the CAPS-5 interview to help determine which event to select as the Index Event. This form is standardly used in conjunction with the CAPS-5 and does not represent a separate assessment.

10. Clinician-Administered PTSD Scale – 5 (CAPS-5). The CAPS-5 is structured interview that assesses the DSM-5 criteria for PTSD (Weathers et al., 2013). Each item is rated on a severity scale ranging from 0 (Absent) to 4 (Extreme/incapacitating) and combines information about frequency and intensity for each of the 20 symptoms. Additional items that are not included in the total score evaluate overall symptom duration, distress, impairment, dissociative symptoms, and global ratings by the interviewer. Validation studies are nearly complete to establish the psychometric properties of the CAPS-5 and findings will be reported in peer-reviewed publications. This interview is very similar to its predecessor, the CAPS for DSM-IV, which has been considered the gold standard for evaluating PTSD and demonstrated good reliability and validity (Weathers, Keane, & Davidson, 2001). In addition to reflecting diagnostic changes for PTSD in DSM-5, the CAPS-5 differs from the CAPS in that frequency and intensity ratings for each symptom are no longer scored separately, so the severity rating for each item determines whether a symptom is present or not. Subscale scores are calculated by summing severity scores for items in the following PTSD symptom clusters: re-experiencing, avoidance, negative alterations in cognitions and mood, and hyperarousal. Scores ≥ 25 indicate a probable diagnosis of PTSD.

11. PTSD Check List – DSM-5 (PCL-5). The PCL-5 (Weathers, et al., 2010) is a 20-item self-report measure update of the PCL designed to assess PSTSD symptoms as defined by the DSM-5. The PCL-5 is currently available and has been shown to have good psychometric properties. The PCL-5 evaluates how much participants have been bothered by PTSD symptoms in the past month (for baseline and follow up assessments) or the past week (all interim assessments) as a result of a specific life event. Each item of the PCL-5 is scored on a five point scale ranging from 0 ("not at all") to 4 ("extremely).

12. Self-Injurious Thoughts and Behaviors Interview- Short Form (SITBI- Short Form). The SITBI-Short Form (Nock, Holmberg, Photos, & Michel, 2007) is a structured interview assessing the presence, frequency, and characteristics of self-injurious and suicidal thoughts and behaviors. The SITBI-Short Form will be administered by an Independent Evaluator, who will instruct the participants to answer the questions based on their entire lifetime of experience. The SITBI-Short Form has shown high interrater reliability, test-retest reliability, and concurrent validity (Nock et al., 2007).

Functional Impairment

13. Health Questionnaire. The original Health Care Utilization (HCU) is a 16-item questionnaire developed in 2000 for Dr. Patricia A. Resick's NIH grant, "Cognitive Processes in PTSD: Treatment II." The questionnaire was based on the 1999 Behavioral Risk Factor Surveillance System. The version that will be administered as part of the STRONG STAR Consortium has been modified to be of increased relevance to active-duty service personnel. The measure includes items regarding use of mental health services, current psychiatric medication, past psychiatric medication, hospitalization, and outpatient medical services, as well as items intended to assess changes in participants' military status.

14. History of Head Injuries. The History of Head Injuries form was developed from the Defense and Veterans Brain Injury Center (DVBIC) 3-Item Screening Tool (Schwab, Baker, Ivins, Sluss-Tiller, Lux & Warden, 2006; Schwab, Ivins, Cramer, Johnson, Sluss-Tiller, Kiley, Lux & Warden, 2006). The DVBIC Screening Tool, initially called the Brief Traumatic Brain Injury Screen (BTBIS), was used as the gold standard for the diagnosis of TBI in a sample of soldiers returning from duty in Iraq and/or Afghanistan (Schwab, Ivins, et al., 2006). As recommended by the DVBIC, the 3-Question Screen will be considered positive when the participant endorses an injury (question 1) and altered consciousness (question 2, items A-E) for the worst head injury sustained while deployed. The form was modified for STRONG STAR and now CAP to capture the number of injuries, and to answer question 2 based on the worst injury; the original form does not recognize the possibility of multiple head injuries during deployment. As the 3-Question Screen does not query head injuries prior to deployment, an additional four questions have been added to solicit information about each head injury sustained outside of deployment.

15. Veterans Rand 12-Item Health Survey (VR-12). Because a certain level of PTSD symptoms is an occupational hazard among service members redeployed for combat, it is critical to pay close attention to functional capacities as an important index of intervention efficacy. The Veterans SF-36 (VR-36) was adapted from the RAND SF-36 Version 1.0 questionnaire, and spans the range of health domains from physical to psychological health status. It

includes two modifications. The first modification is an increase in the number of response choices for the role physical (RP) and role emotional (RE) items from a two point yes/no choice to a five-point likert scale (no, none of the time, yes, a little of the time, yes, some of the time, yes, most of the time, yes, all of the time). The second modification is the use of two items to assess health change, one focusing on physical health and one on emotional problems, in contrast to the one general change item in the RAND SF-36 (Kazis, Lee et al., 2004; Kazis, Miller, Clark et al 2004). The VR-36 has been widely used, distributed and documented in the Veterans Health Administration (VHA) with close to 2 million questionnaires administered nationally in six national surveys since 1996. The changes to the survey have increased the overall precision of the instrument and the discriminant validity of the physical and mental component summary scales (Kazis, Nethercot, et al 2006). The VR-36 is comprised of 37 items and eight scales: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, energy/ vitality, social functioning, role limitations due to emotional problems, and mental health. Also, there are two summary scales: a physical component summary (PCS) and mental component summary (MCS). Higher scores indicate better health. Each summary is expressed as a T score, which facilitates comparisons between the VA patients and the general U.S. population. The PCS and MCS scores provide at least 90% of the reliable variance in the eight SF-36 concepts (Kazis & Wilson, 1998; Kazis, Wilson, et al., 1999). The Veterans SF-12 was developed from the Veterans SF-36 and adapted from the MOS SF-36. It includes fewer items for seven of the eight scales and provides 90% of the reliable variance in the two component summary measures using the Veterans SF-36. Using independent results from the Veterans Health Study and the 1996 National Survey of Ambulatory Care Patients, the results for the Veterans SF-12 corresponded very closely with the results for the Veterans SF-36 (average differences of 0.06 points between them for PCS and 0.31 points for MCS; Kazis et al., 1996; Kazis & Wilson, 1998).

16. Insomnia Severity Index (ISI). The ISI (Morin, 1993) is a 7-item self-report measure that assesses perceived severity of insomnia. Each item uses a 4-point Likert type scale from 0 (not at all satisfied) to 4 (very much satisfied). The items sum to produce a total score (range 0 – 28). The ISI has an internal consistency alpha coefficient of 0.74, and has shown convergent validity with other measures such as the Pittsburgh Sleep Quality Index (r = 0.67), the Dysfunctional Beliefs and Attitudes about Sleep (r = 0.55), and sleep diaries (r ranges from 0.32-0.91) (Bastien, Vallieres & Morin, 2001).

17. PROMIS Sleep-Related Impairment and Sleep Disturbance. The PROMIS Sleep Disturbance and Sleep-Related Impairment short forms (Yu, Buysse, & Germain, 2012) are self-report measures of past-week sleep disturbance and past-week sleep-related impairment, respectively, derived from the larger PROMIS item banks (Buysse et al., 2010). Each short-form measure includes 8 items, with most items (symptoms) scored in intensity from 1 (“not at all”) to 5 “(very much”). Each measure has shown strong reliability and construct validity (Yu et al., 2012).

18. Snoring, Tired, Observed, Blood Pressure (STOP) Sleep Apnea Screen. To better understand sleep disturbance associated with PTSD and PTSD treatment, the STOP screen (Chung et al., 2008) will be administered to screen for sleep apnea. The STOP is a four-item questionnaire developed and validated in 211 pre-operative surgical patients. Based on the endorsement of 2 or more questions, the sensitivity of the STOP ranged from 66% to 80% as compared with the apnea-hypopnea index (AHI) of polysomnography depending upon the AHI cut-off used. Individuals answering “yes” to 2 or more of the questions will be advised that they may be at risk for having sleep apnea and advised that they may want to speak with their primary care provider to consider referral for an overnight sleep evaluation

19. Patient Health Questionnaire – 9 (PHQ-9). The PHQ-9 is a widely used and well-validated instrument for measuring the severity of depressive symptoms (Kroenke, Spitzer, & Williams, 2001). It consists of 9 items that assess both affective and somatic symptoms related to depression and depressive disorders; these 9 items correspond to the diagnostic criteria for DSM MDD. Respondents rate the frequency with which they have been bothered by depressive symptoms within the past two weeks (for baseline and follow up visits) or the past week (for interim assessment visits)on a scale ranging from 0 (“not at all”) to 3 (“nearly every day”). Scores on all items are summed to obtain a total severity score. Scores reflect no significant depressive symptoms (0-4), mild depressive symptoms (5-9), moderate depressive symptoms (10-14), moderately severe depressive symptoms (15-19), and severe depressive symptoms (>19). Respondents also indicate the degree to which their depressive symptoms have made it difficult for them to do their work, take care of things at home, or get along with other

people, from “not difficult at all” to “extremely difficult.” The PHQ-9 has high internal consistency (e.g., alpha ranging from .83 to .92; Cameron, Crawford, Lawton, & Reid, 2008), and correlates strongly with other measures of depression (Kroenke et al., 2001).

20. Fagerstrom Test for Nicotine Dependence (FTND). The FTND (Heatherton et al., 1991) is a 6-item self-report measure that assesses severity of nicotine dependence. Questions probe both quantity of nicotine use (e.g., number of cigarettes per day) and pattern of use (e.g., time to first cigarette in morning). Respondents choose among response options, each of which is assigned a numerical value, with higher numbers corresponding to greater nicotine dependence. Scores on all items are summed to create a severity index (0-2 = very low dependence; 3-4 = low dependence; 5 = medium dependence; 6-7 = high dependence; 8-10 = very high dependence). The Fagerstrom scale has been shown to have high convergent validity with biochemical indices of nicotine use, and the measure has shown acceptable internal consistency (Heatherton et al., 1991). A review of 26 studies of the psychometric characteristics of the Fagerstrom found that it is a reliable instrument for measuring nicotine dependence in diverse settings and populations (Meneses-Gaya et al., 2009).

21. Fagerstrom Test for Nicotine Dependence- Smokeless Tobacco (FTND-ST). This is a modified version of the Fagerstrom Test that focuses on smokeless tobacco use, whereas the original Fagerstrom focuses exclusively on smoking. Like the FTND, the FTND-ST is a 6-item self-report measure of severity of nicotine dependence that has demonstrated convergent validity with biochemical indices of nicotine use (Ebbert et al., 2006; Ferketich et al., 2007). As on the original FTND, respondents choose among response options, each of which is assigned a numerical value, with higher numbers corresponding to greater nicotine dependence. Scores on all items are summed to create a severity index (range = 0–10).

22. Alcohol Use Disorders Identification Test (AUDIT). The AUDIT (Babor et al, 2001) will be used to identify people with hazardous or harmful patterns of alcohol consumption. The AUDIT is a 10-item screening measure, developed by the World Health Organization (WHO), with three subscales (alcohol consumption, drinking behavior, and alcohol-related problems) that are scored on a 4-point scale for a highest possible total score of 40. Among those identified as using alcohol in a harmful manner, 92% had scores of 8 or more, though determining a cutoff score should be left up to the clinician, depending upon the population being studied. The AUDIT has good internal consistency (α = .80-.93) as well as sensitivity and specificity (Saunders, Aasland, Babor, De La Fuente & Grant, 1993).

23. Quick Drinking Screen (QDS). The QDS (Sobell et al., 2003) will be used to measure alcohol consumption. It consists of 4 items probing frequency and quantity of alcohol consumption. It will be administered in a self-report form. The QDS has been validated against the Timeline Followback daily estimation measure of alcohol use, and it shows good psychometric properties (Roy et al., 2008; Sobell et al., 2003). The QDS’s time-frame will be modified to match the “last two weeks” probed by the mandated depression and anxiety instruments for CAP studies (PHQ-9 and GAD-7). Like these other measures, the QDS can be administered frequently throughout CAP trials to track changes in alcohol use.

24. Mini-International Neuropsychiatric Interview (MINI)- Manic and Psychosis modules. The MINI 7.0 is a short, structured clinical diagnostic interview designed to cover the major psychiatric disorders in DSM-5 and ICD-10. It is widely used in epidemiological studies and multi-site clinical trials. Responses to the interviewer’s questions are rated as either “yes” or “no.” As is the case on the SCID, there are skip-outs, which saves time. However, this means that the MINI cannot be used to index the severity of a given psychiatric problem, only caseness. When there are many skip-outs, the MINI takes ~15 minutes to administer. The MINI can be used to assess the full spectrum of psychiatric problems, or specific modules can be employed (e.g., the schizophrenia module to rule out thought disorder).

25. Tinnitus Functional Index (TFI). The Tinnitus Functional Index (TFI) was reported by Henry et al (2014). They report five stages of TFI development through which prototypes were developed, tested, and revised over a four-year period. The TFI has eight subscales that address the intrusiveness of tinnitus, the sense of control the patient has, cognitive interference, sleep disturbance, auditory issues, relaxation issues, quality of life, and emotional distress.

26. Tinnitus Acceptance Questionnaire (TAQ). The Tinnitus Acceptance Questionnaire (TAQ) was reported by Westin et al. (2008). This measure captures the extent to which individuals accept their tinnitus, and attempts to avoid or control tinnitus, as well as a patient's ability to pursue valued life activities and meaningful goals regardless of tinnitus. The TAQ was further validated in an English speaking population (Weise et al., 2012).

Psychosocial Functioning

27. Brief Inventory of Psychosocial Functioning (BIPF). The Brief Inventory of Psychosocial Functioning (Marx et al. 2013) is a 7-item self-report instrument measuring respondents' level of functioning in seven life domains: romantic relationship, relationship with children, family relationships, friendships and socializing, work, training and education, and activities of daily living. Respondents indicate the degree to which they had trouble in the last 30 days in each area on a 7-point scale ranging from "0 = Not at all" to "6 = Very much."

Other Key Mediators & Moderators

28. Homework Compliance. The Homework Compliance form asks questions about how often participants used the worksheets, how many minutes were dedicated toward the practice assignments, and how helpful the practice assignments were considered.
29. Resting-state fMRI. Resting state *f*MRI techniques (Adhikari et al., 2018) will be conducted among individuals with comorbid PTSD and tinnitus. Resting-state connectivity will be assessed by mapping inter-regional connectivity using an extended time series BOLD *f*MRI images acquired in an unstimulated state. Connectivity can be detected and quantified using inter-connected regions, which show temporally correlated variations and are analyzed with a data-driven analytic strategy called Independent Components Analysis. Resting-state networks that will be examined include the default-mode network, auditory network, limbic network, and attentional network.

Appendices:

A – CPT Treatment Manual
B – Recruitment Flyer
C - Telephone Script and Pre-Screen Questionnaire
D – MRI Prescreening Video
E – MRI Prescreening Video Script
F – Explanation for Tinnitus and PTSD (to be discussed during session 1)