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Official Study Title:
An Evaluation of Neurobiological Similarities of Tinnitus and Posttraumatic Stress Disorder

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HUMAN SUBJECTS RESEARCH PROTOCOL

1. PROTOCOL TITLE: An Evaluation of Neurobiological Similarities of Tinnitus and Posttraumatic Stress Disorder

2. ABSTRACT

Past neuroimaging research demonstrates the role of the auditory system in tinnitus, which is highly comorbid and shares symptoms with PTSD. The latest findings from a STRONG STAR neuroimaging study indicate that the auditory system is also the most highly implicated resting-state brain network among individuals with combat-related PTSD (Vanasse et al., 2019). These findings provide a compelling argument that an underlying neurobiological mechanism contributes to comorbid tinnitus and combat-related PTSD, suggesting a different phenotype for this comorbidity. A different phenotype may explain non-responsiveness to trauma-focused therapy, causing a significant public health concern. Finding neurobiological markers of both disorders will prompt novel behavioral and neuro-modulatory therapies to target and regulate specific brain networks.

To assess these conditions, we will use group information-guided independent components analysis (GIG-ICA; Du et al., 2015; Du & Fan, 2013), a neuroimaging statistical discovery method optimized to detect between-group differences. These analyses will determine specific brain regions within the auditory network that are common and unique to tinnitus and PTSD; we will map these regions with corresponding symptoms. Others found a single network between the auditory (A-1) and ventral attention (VAN) networks (Yeo et al., 2011), which explains startle responses among PTSD patients. We will refer to this unified network as the auditory-vigilance network (A1/VAN), which will be the focus of this project.

3. OBJECTIVES/SPECIFIC AIMS/RESEARCH QUESTIONS

Objective:
The scientific goals of this proposal are to further characterize tinnitus and PTSD symptomatically (Aim 1), neurobiologically characterize tinnitus and PTSD, independently and conjointly (Aim 2), and apply modeling to psychometric and neurofunctional data (Aim 3). We will recruit veterans and active duty service members with tinnitus and PTSD, PTSD only, tinnitus only, and healthy controls. We will assess participants for PTSD, tinnitus, hearing loss and other audiologic disorders, and conduct resting-state functional magnetic resonance imaging (rs-fMRI).

Specific Aim 1: To further characterize the cognitive, behavioral, and emotional symptoms associated with both tinnitus-related distress and PTSD.

Hypothesis 1: Canonical correlations will identify both shared and unique symptoms between tinnitus-related distress and PTSD.

Specific Aim 2: To identify the functional connectivity patterns in the auditory-vigilance network associated with both tinnitus and PTSD.

Hypothesis 2a: Dysregulated connectivity within the auditory-vigilance resting state network will be implicated among individuals with both tinnitus and PTSD.

Hypothesis 2b: Individuals with tinnitus and PTSD will demonstrate unique patterns of dysregulation within the auditory-vigilance network versus those with only PTSD, only tinnitus, and healthy controls.

Specific Aim 3: To identify specific regions within the auditory-vigilance network that correspond with tinnitus-related distress and PTSD symptom severity.

Hypothesis 3: Dysregulated activity within regions of the auditory-vigilance network will be correlated with symptom

clusters of both tinnitus-related distress and PTSD.

HUMAN SUBJECTS RESEARCH PROTOCOL

4. BACKGROUND AND SIGNIFICANCE.

Tinnitus and PTSD at the Symptom/Impairment Level

At the symptom and impairment levels, research supports the notion of shared mechanisms between tinnitus and PTSD, including (1) overlapping symptoms between tinnitus-related distress and PTSD; (2) comorbidity between tinnitus and PTSD; and (3) functional outcomes of individuals with both disorders.

Overlapping Symptoms and Comorbidity. The same traumatic event could cause PTSD and tinnitus (e.g., IEDs). Tinnitus can be conceptualized as a conditioned stimulus, reminding the individual of the traumatic event (Criterion B of PTSD; APA, 2013), as in flashbacks (Hinton et al., 2006). Those with tinnitus also show symptoms of avoidance (Criterion C of PTSD). Veterans with both tinnitus and PTSD, and those with only tinnitus, reported similar aversions to loud signals and lower tolerance to loud noises (Fagelson, 2007), which may result in decreased social interaction and engagement in pleasurable activities (Jastreboff & Jastreboff, 2002). Negative alterations in mood and cognition (Criterion D of PTSD) are observed in those with tinnitus, and tinnitus-associated trauma and catastrophic cognitions predict PTSD severity (Hinton et al., 2006). Finally, individuals with tinnitus show emotional reactions that overlap with vigilance or hyperarousal (Criterion E of PTSD), including startle responses, anger, and irritability (Fagelson & Smith, 2016), and sleep disturbance (McKenna, 2000). The high comorbidity between tinnitus and PTSD also suggests a common etiology that leads to impairment and distress. Our recent study (Moring et al., 2020a) found a latent factor between tinnitus-related distress and PTSD symptoms among veterans with PTSD, tinnitus, and posttraumatic headache. Based on this evidence, we posit that PTSD exacerbates impairment among individuals with tinnitus. More research is needed to investigate psychiatric contributions to tinnitus-related distress, such as PTSD, with a possible unique phenotype when tinnitus and PTSD co-occur.

Functional Outcomes. Functional outcomes for those with both tinnitus and PTSD are significantly worse than those with tinnitus only, or tinnitus and any other psychological disorder (Fagelson & Smith, 2016). This suggests a particularly deleterious combination of symptoms that exacerbate, and possibly maintain each disorder. It is feasible to treat psychiatric distress, and if successful, tinnitus-related distress will also decrease. Civilians with tinnitus had less tinnitus-related distress after receiving trauma-focused therapy (Rikkert et al., 2018), but they were not evaluated for PTSD. These studies demonstrate the association between tinnitus and PTSD. More research is warranted to elucidate the neurobiological mechanisms of both tinnitus and PTSD.

Comorbid Tinnitus and PTSD at the Neurobiological/Network Level

The auditory network-1 (A-1) is highly implicated among PTSD patients. In fact, the auditory network contains the most regions that differentiate veterans with PTSD and veterans exposed to combat versus civilian controls (**Figure 3**; Vanasse et al., 2019). Regions within A-1 included the supramarginal gyrus, mid temporal gyrus, inferior frontal gyrus, insula, precentral gyrus, cingulate gyrus, sub-gyral, and the superior temporal gyrus (Laird et al., 2011). These brain areas are also considered as part of the ventral attention network (VAN; Yeo et al., 2011), known for stimulus saliency. Therefore, the network was labeled the Auditory Vigilance Network (A1/VAN), and explains symptoms of Criterion E of PTSD (Alterations in Arousal and Reactivity). These symptoms include irritability, hypervigilance, startle responses, concentration issues, and sleep problems, also common among those with tinnitus. However, Vanasse et al. (2019) did not assess for tinnitus. Other research findings implicate the A1/VAN network in modulating other networks among PTSD patients. One study found lower connectivity involving the A1/VAN and other regions of separate resting-state networks, including the amygdala and prefrontal cortex (Shang et al., 2014). There was also higher connectivity between the A1/VAN and the visual cortex, which may explain vivid intrusive memories often experienced by PTSD patients. However, the extent to which these results generalize to individuals with comorbid tinnitus and PTSD is unknown.

Neurobiological Mechanisms of Tinnitus

The A1/VAN network is the most frequently implicated network in patients with tinnitus (De Ridder et al., 2014; Hussain, 2016; Lv et al., 2017; Pattyn et al., 2016). However, it does not function independently of other resting-state brain networks, but instead modulates hypo-or hyper-activity among other networks. The primary auditory cortex, within A1/VAN, and the occipital/visual cortex are negatively correlated among tinnitus patients versus controls (Burton et al., 2012), suggesting extensive changes to the integrities of other networks. In our recent meta-analysis, the left cingulate gyrus, right inferior frontal gyrus (BA 44 & BA 45), and right insula were significantly more dysregulated in those with

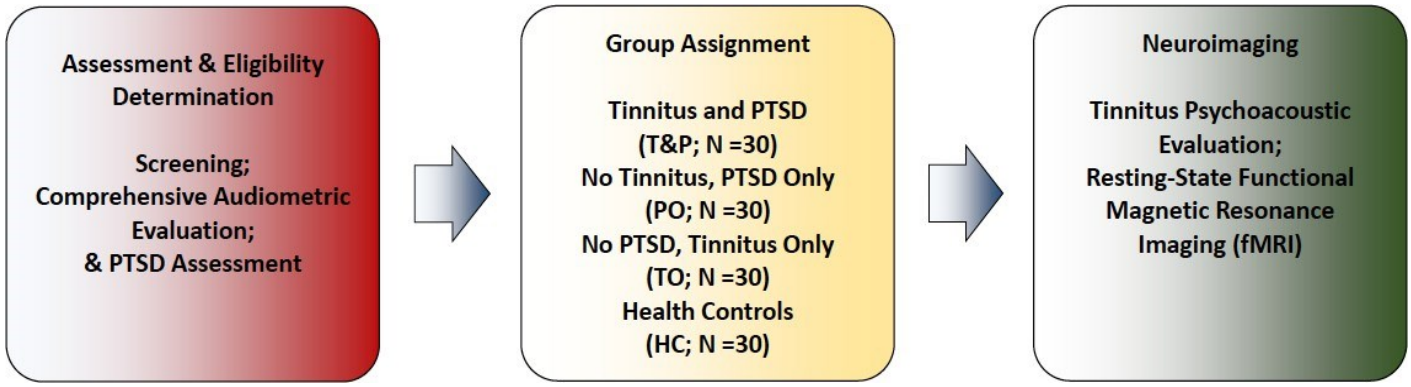
tinnitus versus controls (Moring et al., 2020b). These regions are within the A1/VAN resting-state network and overlap with regions implicated in combat-PTSD patients (Vanasse et al., 2019). Other studies of individuals with tinnitus have reported enhanced functional connectivity (FC) between A1/VAN and the attention network (Kim et al., 2012), default mode network, and the dorsal attention network (Schmidt et al., 2013). The amygdala and parahippocampus have shown heightened connectivity to A1/VAN (Carpenter-Thompson et al., 2014), and is likely dependent upon tinnitus severity (Husain, 2016).

We hypothesize that combat experiences, including stress and noise, alter functional connectivity within the A1/VAN. This dysregulation contributes to tinnitus or PTSD, or both, resulting in common symptoms and clinical presentations. A1/VAN modulates hypo- and/or hyperactivity within other brain networks, resulting in symptoms of tinnitus and/or PTSD. We hypothesize that the A1/VAN is a privileged network with a central role in the hypo- or hyper-activation of other networks, directly or indirectly; thus, it influences tinnitus sensation, tinnitus-related distress, and PTSD. Dysregulation of specific brain regions within A1/VAN is the neurobiological mechanism responsible for comorbid tinnitus and PTSD, and suggests a different phenotype among such individuals, which may help explain high rates of non-response to PTSD treatment (Steenkamp & Litz, 2020). We will examine the overlapping and unique symptoms between both disorders, the neurobiological similarity between tinnitus and PTSD, and model psychometric and neurofunctional data.

5. RESEARCH DESIGN

We propose a phenotyping and neuroimaging study, examining shared and unique symptoms and neurobiological contributions for tinnitus and PTSD. We will recruit individuals with both tinnitus and PTSD (**T&P**), PTSD Only (**PO**), Tinnitus Only (**TO**), and Healthy Controls (**HC**) (30/group). After consent is provided, participants will be scheduled for audiometric evaluations and PTSD assessment to determine eligibility. Eligible participants will be assigned to one of the four groups and scheduled for an additional tinnitus psychoacoustic evaluation, when available, to demonstrate reproducibility. Resting-state fMRI (rs-fMRI) scans will be completed at this time. Study-related procedures will be completed within 4 weeks to decrease likelihood of drop-out.

Figure 1. Study Design Overview.



6. RESEARCH PLAN

6.1 Selection of Subjects

6.1.1. Subject Population.

This study will consent and screen 160 veterans and active duty service members to include 120 for analysis. Subjects will be recruited from the San Antonio community. Women and minorities will be actively recruited into the study.

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

- Male and female DEERS eligible veterans and active duty service members, ages 18 and above
- preferred language is English and able to read and speak English at a 6th grade level
- those with PTSD (T&P; PO) must meet full criteria for PTSD diagnosis based on the DSM-5 and assessed by an independent evaluator using the CAPS-5
- those with chronic, constant tinnitus (T&P, TO) will be identified by self-report and confirmed with the audiometric assessment.

Exclusion Criteria

- psychiatric hospitalization in the last 12 months
- significant cognitive impairment determined by inability to comprehend screening assessment
- psychiatric problems and/or high suicide risk warranting immediate intervention
- neurobiological disorders, Meniere's disease
- Temporomandibular disorders that affect tinnitus, per self-report
- history of major head trauma with loss of consciousness for 20 minutes or more as determined by the History of Head Injuries questionnaire
- history of seizures
- conditions that would prevent completion of fMRI scan (any type of electronic, mechanical, or magnetic implant, coil, filter, or stent, any type of surgical clip or staple, shunt, any type of metal object, hearing aid, spinal fusion, halo vest, IV access port, eyelid spring, artificial eye, artificial heart valve, biostimulator, severe hyperacusis)
- active conductive pathology/hearing loss as determined by audiometric assessment.
- Those with tinnitus (T&P; TO) will be excluded if their tinnitus is
    - intermittent
    - objective or pulsatile
    - present for less than 6 months.

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. One additional flyer will be posted to target potential participants who do not meet criteria for PTSD and/or tinnitus. Potential participants may also self-refer in response to recruitment information on the STRONG STAR website and social media. 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. Approved flyers will be posted within Brooke Army Medical Center and affiliated clinics, including primary care, preventive care, auditory, dental, pharmacy, CPT Jennifer Moreno Primary Care Clinic, and Westover Medical Home, after appropriate clinic approval is obtained. 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 a "consent to contact" form (Appendix A) from interested individuals so that study staff can contact them directly about study participation. In addition, there may be community events where information about STRONG STAR studies is provided and those interested may fill out the "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 (Appendix B).

Under an IRB approved HIPAA Waiver of Authorization, study personnel will conduct a brief telephone pre-screening or in-person 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 B). 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 individual 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 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.

Individuals 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, either the first audiometric assessment or diagnostic interview will be completed. If not interested or phone screened out from this study, individuals 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 using a paper form at the STRONG STAR offices or at the Hearing Center of Excellence or online using an electronic consent (eConsent). The preferred method is to use the eConsent process. Potential participants will be provided a link to the informed consent document (ICD) or will be given a hard 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, a member of the study team will review the risks and benefits of study participation and ensure the participant has an understanding of the material discussed, and the risks and benefits of their potential involvement in the study. The participant will sign the consent form either electronically or on a paper form. A copy of the signed ICD will be given to the participant.

6.1.6. Subject Screening Procedures.
Following consent, screening and assessment will take place to determine participant eligibility. The entire screening process will take approximately 5 hours. This will include the completion of the questionnaires and interviews outlined in the table in Section 6.2 below. This may occur in-person using paper forms or the participant will be logged into the STRONG STAR eCAP online data capture system to complete self-report questionnaires. For individuals not meeting study inclusion criteria, the Study Staff will assist coordinating appropriate care outside of the study.

If the participant has been referred from another STRONG STAR study and already completed assessments within the past 30 days, the participant will be asked as part of the consent process to use these assessments rather than repeating the assessment battery. If the participant is newly referred to this study, if it has been more than 30 days since completing the assessments for another study, or the participant declines use of previously completed assessments, he or she will meet with an evaluator and complete the full baseline assessment per protocol.

6.1.7. Compensation for participation.
In accordance with the Defense Health Agency (DHA) Administrative Instruction (AI) Number 3200.01 dated 28 April 2022, all study participants will be compensated $50 for the neuroimaging scan. As outlined in the DHA AI, for active duty participants to receive compensation, they must not otherwise be scheduled to perform work during the neuroimaging scan appointment. 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.

6.2. Study Procedures and Description of Assessments

A trained research staff member will explain the study to potential participants in a private location and give them a copy of the informed consent document to read. The staff member will review the risks and benefits of the study and ensure the potential subject understands the research. Once consent is given, the screening assessments will then be scheduled. Timing of assessments will be determined by participants' availability. Group assignment, main outcomes, and participant characterization measures are described below. **Table 1** lists assessments.

Group Assignment

Participants will be assigned to one of four groups, based on results of audiometric assessments and the Clinician Administered PTSD Scale for DSM-5 (CAPS-5), explained below. Those who indicate they have bothersome tinnitus and meet criteria for PTSD on the CAPS-5 (conducted by an independent evaluator), will be assigned the Tinnitus and PTSD Group (**T&P**). Those who do not endorse tinnitus and meet criteria for PTSD will be assigned to the PTSD Only Group (**PO**). Those who indicate they have bothersome tinnitus but do not meet criteria for PTSD will be assigned to the Tinnitus Only Group (**TO**). Those who do not endorse tinnitus and do not meet PTSD criteria on the CAPS-5 will be assigned to the Healthy Control Group (**HC**). All will then be scheduled for an fMRI scan. Participants will be matched across groups for sex, age, head injury, length of military service, number of deployments, and hearing loss. Measures used for group assignment and characterization are explained below.

Assessment Instruments.

The audiometric assessments will be conducted at the Hearing Center of Excellence (60 minutes). Repeat tinnitus acoustic assessment only (see description below) may be completed at the RII prior to the fMRI for eligible participants with tinnitus when an evaluator is available (30 minutes).

Self-report instruments may be administered at the Hearing Center of Excellence, at the STRONG STAR offices, or via online data capture, Clinical interviews may be administered at the STRONG STAR offices or via phone or video conferencing. These assessments are estimated to take approximately 90 minutes.

fMRI scans will be conducted at the Research Imaging Institute (60-75 minutes). Participants will be asked whether they hear their tinnitus before the MRI scan, whether they heard the tinnitus during the scan, and whether their tinnitus changed since the last time asked.

All assessments will be conducted within a 4-week time-frame. Instruments are explained below.

1. The Demographics and Military Service Characteristics Form gathers information about age, sex, educational background, marital status, military status and rank, and number of deployments.

2. 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.

3. MRI Screening Questionnaire will be used to exclude those with conditions that could interfere with completing the fMRI scan.

4. 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).

5. The Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5; Weathers, et al., 2013) is a semi-structured interview, conducted by an independent evaluator, that measures *DSM-5* symptoms of PTSD. Presence of at least one intrusion symptom, one avoidance symptom, two cognition and mood symptoms, and two arousal symptoms for 1 month or more are required to reach the diagnostic threshold. Selection of Index Event for CAPS-5 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. The CAPS-5 will be used to determine whether participants meet criteria for PTSD for group determination and is a central variable in the study.

6. 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) 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).

7. The Tinnitus Functional Index (TFI; Meikle et al., 2011) has documented validity for scaling the severity and negative impairment of tinnitus for use in intake assessment, and for responsiveness to treatment. The TFI will be used to determine group assignment and to control for tinnitus-related distress in analyses.

8**. Resting-State Functional Magnetic Resonance Imaging** (rs-fMRI). We will acquire BOLD fMRI images in an unstimulated state using an extended time-series (300 whole-brain volumes over ~ 60-75 min). These data are a main outcome. Data will be processed on an ongoing basis to ensure integrity, and includes controlling for white matter, cerebral spinal fluid, and movement.

9. Hyperacusis Questionnaire (HAQ). The Hyperacusis Questionnaire (HAQ; Khalfa et al., 2002) is a self-report questionnaire that evaluates various hyperacusis symptoms. The HAQ consists of three factors, including attentional, social, and emotional dimensions of hyperacusis. All three dimensions have satisfactory internal consistency reliability.

10. Audiometric Assessment. All audiometric testing will occur at the HCE in a double-walled, sound-isolated chamber adjacent to a control room. Participants will be instructed to abstain from loud noises, to the extent possible, for 14 hours prior to the appointment (OSHA Occupational Noise Exposure standard). Results will be used to exclude participants with intermittent, objective or pulsatile tinnitus. Results will also be used to characterize and control for tinnitus pitch and loudness (thresholds measured by dB and frequency measured by Hz), frequency and level of hearing loss (measured by Hz and dB, respectively), and other audiology disorders for analyses.

i. Tinnitus and Hearing Healthcare Questionnaire - The Tinnitus & Hearing Questionnaire is a 23-item questionnaire that obtains descriptive information about individuals' tinnitus (pitch, loudness, sound) and extent of hearing loss. Items also assess individuals' perspective concerning the etiology of their tinnitus and hearing loss, and health information that may exacerbate or attenuate tinnitus-bothersomeness. This questionnaire also assesses whether participants have had COVID-19, and whether their symptoms were mild, moderate, or severe.

ii. Otoscopy will be performed before audiologic testing.

iii. Tympanometry will be conducted to assess ear canal volume (cm cubed), maximum pressure (daPa) peak compliance (ml), and type (A, AD, AS, B, B-High, C) for each ear) at 226-Hz admittance.

iv. Pure tone air- and bone-conduction threshold will be conducted to evaluate audiometry and masking levels in both ears, from 250 Hz. To 16000 Hz.

v. Speech testing will be conducted in both ears, which will include speech reception threshold, speech reception threshold masking level, word recognition presentation level, and word recognition masking level.

vi. Loudness discomfort levels will be tested in both right and left ears, from 500Hz to 4000Hz and speech reception threshold.

vii. Quick Speech in Noise Test (QuickSIN) is a quick method for clinicians to quantify a patient's ability to hear in noise (1 minute).

viii. Tinnitus acoustic assessment (for tinnitus participants only): Tinnitus ear (left, right, bilateral), pitch matched frequency (Hz) and loudness matched intensity (dB) will be conducted. When available, the tinnitus acoustic assessment only will be repeated at the RII, on the same day and prior to the fMRI scan, to demonstrate reproducibility of results.

ix. Distortion-Product Otoacoustic Emissions (DPOAE) is an automated evaluation of cochlear function. A sensitive microphone is placed in the ear canal via a probe assembly with a disposable ear-tip attached to perform and record the measurements. DPOAEs will be elicited at multiple frequencies in both ears (10 min).

Measures for Group Characterization

1. **Health Questionnaire** which includes items regarding general health, current psychiatric medications, and use of mental health services and outpatient medical services.

2**. 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).

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**. 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.

6**. 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).

7**. 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).

8**. 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).

Table 1 **Measures and Assessments**	**Time (Min)**	**Aim**
Screening Assessments and Main Outcomes		
1. ^Demographics and Military Service Characteristics Form	5	I/E
2. *History of Head Injuries	5	I/E
3. ^MRI Screening Questionnaire	5	I/E
4. ^Life Events Checklist (LEC)	5	I/E
5. *Clinician-Administered PTSD Scale – 5 (CAPS-5)	50	1,2,3
6. ^PTSD Checklist (PCL-5)	5	1,2,3
7. ^Tinnitus Functional Index (TFI)	5	1,2,3
8. *rs-fMRI Scan & Tinnitus Data Collection Page	60-75	2,3
9. ^Hyperacusis Questionnaire (HAQ)	5	I/E
10. *~Audiometric Assessment -Tinnitus & Hearing Healthcare History Questionnaire, tympanometry, pure tone air- and bone-conduction, speech testing, loudness discomfort, quick speech in noise test, tinnitus evaluation, & DPOAE	60	I/E
11. ~Repeat Tinnitus Assessment when available	30	-
Group Characterization Measures		
1. ^Health Questionnaire (HQ)	10	-
2. ^Alcohol Use Disorders Identification Test (AUDIT)	5	-
3. ^Deployment Risk and Resilience Inventory (DRRI-2) Combat Experience	5	-
4. ^Deployment Risk and Resilience Inventory (DRRI-2) Postbattle Experiences	5	-
5. ^Trauma Related Guilt Inventory (TRGI)	5	-
6. ^Generalized Anxiety Disorder-7 (GAD)	5	-
7. ^Patient Health Questionnaire – 9 (PHQ-9)	5	-
8. ^Tinnitus Acceptance Questionnaire (TAQ)	5	-
Total Time (Min) over three visits	280 - 295	-
*Conducted by independent evaluator, MRI technician, or audiologist; ^Completed by the participant; I/E= inclusion/exclusion criteria; ~Completed by Participant		

6.3.2 Data Collection.

6.3.2.1 Instrumentation:
See the table at Section 6.2 above for a summary and description of the assessments and timing of administration. A description of each of the assessments can be found in the previous section of this protocol. Assessments will be administered in person whenever possible. However, we may collect assessments in person, via phone, video conferencing, and/or electronic data capture using a secure link to the encrypted STRONG STAR database.

6.3.2.2. Resting state *f*MRI.
Participants who are eligible to continue in the study after consent and screening will undergo a resting-state function magnetic resonance imaging (rs- fMRI) 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. Each MRI scan may take up to 75 minutes. Participants will be asked whether they hear their tinnitus before the MRI scan, whether they heard the tinnitus during the scan, and whether their tinnitus changed since the last time asked. Data will be recorded on the Tinnitus Data Collection Page.

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; the Research Imaging Institute (RII), or the Hearing Center of Excellence at Wilford Hall Ambulatory Service Center at Lackland Air Force Base (HCE). Data collected will be entered into a spreadsheet located on a secure STRONG STAR server. Audio-recordings of assessments 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. Audiometric data will be kept under lock and key at the HCE. 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.

6.4 Statistical Consideration

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

Primary outcomes include results based 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 measures of depression and suicide (PHQ-9), anxiety (GAD-7), and alcohol use (AUDIT).

6.4.2 Hypotheses, Sample Size Estimation, and Specific Data Analysis Plans.

Hypothesis 1: Canonical correlations will identify both shared and unique symptoms between tinnitus-related distress and PTSD.

Analysis Plan: Non-inferential statistics will be calculated to include central tendencies, standard deviations, and alpha coefficients. Prior to analyzing data, unusual distributions, missing data, or outliers will be identified. Descriptive statistics will be used to summarize participant characteristics. Group differences will be tested using t-tests, Chi-Square, or Fisher's exact tests as needed. Canonical correlations will be conducted on the data of all 60 participants from the T&P and TO groups, using the subscale scores of the CAPS-5 and the TFI. Canonical correlations identify and measure associations among two sets of variables and will identify latent variables between tinnitus-related distress and PTSD symptoms. The 12 total subscales from the CAPS-5 and TFI will be entered into the analyses, requiring 60 participants for large effect sizes (Steven, 1986).

Hypothesis 2a: Dysregulated connectivity within the auditory-vigilance resting state network will be implicated among individuals with both tinnitus and PTSD.
Hypothesis 2b: Individuals with tinnitus and PTSD will demonstrate unique patterns of dysregulation within the auditory-vigilance network, versus those with only PTSD, only tinnitus, and healthy controls.

Analysis plan: rs-fMRI provides valuable information about neurobiological mechanisms that influence neurological and psychiatric conditions at rest (Menon, 2011). To test our conceptual model and deduce neurobiological mechanisms, we will use an existing, well-documented, 20-component parcellation scheme of the resting-state networks (Laird et al., 2011; Auditory Component 16). After extracting the A1/VAN, we will use group information-guided independent components analysis (GIG-ICA) to determine intra-network connectivity differences between those with both tinnitus and PTSD, only PTSD, only tinnitus, and healthy controls. Our team (Vanasse et al., 2019) found robust differences between active-duty service members with PTSD, combat controls, and civilian control (50 active-duty with PTSD, 28 combat-exposed controls, and 25 civilian controls). Based on those results, 120 participants (30 per group) in this proposed study, *a priori* power analyses demonstrated power of 80% when $\alpha = 0.05$, to detect an effect size of $d = 0.31$ (ANOVA: Fixed effects, omnibus one-way; Faul et al., 2007). Secondary analyses will examine functional connectivity between A1/VAN and other resting-state networks.

Hypothesis 3: Dysregulated activity within regions of the auditory-vigilance network will be correlated with symptom clusters of both tinnitus-related distress and PTSD.

Analysis plan: Correlations will be conducted between functional connectivity within the auditory-vigilance resting state network with tinnitus-related distress and PTSD symptoms. Power analyses predict that 57 participants will achieve a power of .95, with an effect size d = .45, and alpha = .05 (R Core Team, 2014).

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.

6.5 Confidentiality

All in-person interview assessments will be delivered in private offices at the STRONG STAR Clinic or RII at the UTHSCSA, or the HCE. This study involves remote and/or virtual research interactions with participants by the research staff. Research activities will be audio-recorded by an independent device (separate from the conferencing platform, i.e. Zoom). Therefore, privacy and confidentiality is not guaranteed due to the nature of the electronic conferencing platforms that will be used. Data will be stored by an assigned participant code number. Digital audio recordings of assessments 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.

6.5.1 Certificate of Confidentiality.

We are not seeking a Certificate of Confidentiality.

6.5.2. Data Protection. Data will be coded using an assigned number. Assessments will be stored in a locked cabinet at the STRONG STAR Clinic at the UTHSCSA, the RII, or HCE. Digital audio recordings of assessments will be labeled with the participant's study id number and uploaded onto the secure STRONG STAR server.

7.0 RISKS/BENEFITS ASSESSMENT

7.1 Risks.

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 Assessment of PTSD

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

- The assessment of PTSD and trauma-related events may produce some discomfort or emotional distress and can even produce a temporary increase in PTSD symptoms.

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).
- Hyperacusis. Individuals with hyperacusis who are sensitive to noise may experience some distress related to. the loudness of the fMRI procedure.

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

- Identification of incidental, asymptomatic lesions of unknown significance
  Occasionally, previously unsuspected lesions that are not causing any symptoms may be found as a result of the research scan. In these instances, a member of the Research Team (Principal Investigator: Moring) will contact the participant, explain the abnormality that was found and give copies of the scans to the participant. The participant will be encouraged to visit with their primary care provider to see if any action should be taken. A follow-up letter that describes the incidental findings will be mailed to the participant.
- 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 , we will ask participants about any metal objects that may be in their body in order to ensure their safety.

Safeguards for Protecting Participants: One of the risks with assessment of mental health conditions is identification of suicidality or harm of others. Participants will be provided immediate coping tools and techniques used to manage distressing emotions by a licensed 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: 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 allowed to remain in the study but will be referred to the research audiologist or primary care provider as applicable for appropriate follow up within standard of care. For participants identified as being at high risk for suicide based on the assessment results, they will be excluded from the study and will be referred for more intensive treatment (outpatient or inpatient).

The diagnostic assessment testing may also indicate PTSD symptoms, anxiety, depression, or alcohol use that warrants treatment. Additionally, unsuspected lesions or hearing changes may be found as a result of the research testing. In these instances, a member of the Research Team will contact the participant, explain the test findings and, if appropriate, encourage the participant to see their primary care provider. The research testing is not being done to diagnose health problems, and so the participant will need to see their primary care provider to see if any action should be taken. The research team can help facilitate communication with the primary care provider and provide local resources. For active duty personnel, the military command will NOT be notified, and the results of the research testing will NOT be placed in the medical record.

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.

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 and service members. Results may provide a compelling argument that an underlying

neurobiological mechanism contributes to comorbid tinnitus and combat-related PTSD, suggesting a different phenotype for this comorbidity. A different phenotype may explain non-responsiveness to trauma-focused therapy, causing a significant public health concern. Finding neurobiological markers of both disorders will prompt novel behavioral and neuro-modulatory therapies to target and regulate specific brain networks.

7.3 Alternatives:

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

Treatments for tinnitus are available include the following:

- Acceptance and Commitment Therapy
- Progressive Tinnitus Management
- Tinnitus Retraining Therapy
- Cognitive Behavioral Therapy for 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 given appropriate treatment referrals. If participants are discontinued due to a serious adverse event, they will continue to be followed clinically by the PI and/or member of the research staff until the adverse event is resolved or becomes stable. The reason the participants are discontinued from the study and any referrals made will be documented.

10.0 LONG-TERM DATA STORAGE.

A STRONG STAR Repository has been approved by both the UTHSCSA (HSC20100475H) IRB to enable the STRONG STAR Consortium to store specimens and data for future use. The STRONG STAR Repository will create a large comprehensive database of information, biological specimens and neuroimages related to the identification, assessment, and treatment of PTSD in our active duty and retired veterans of conflicts following 9/11. All information entered into the

STRONG STAR Repository will be extracted from primary datasets collected as part of IRB-approved studies, including this study, being conducted and /or supported by the projects of the STRONG STAR Consortium. These study databases will be established and maintained by the Biostatistics and Data Management Core of the STRONG STAR Consortium. A unique, sequential alpha-numeric STRONG STAR ID will be assigned to each participant at the time of recruitment into this study. However, all Repository data will be identified with a different code number that can be cross linked to the original study code only through records maintained by the STRONG STAR Biostatistics and Data Management Core. Data, biological specimens and images will constitute the STRONG STAR PTSD Repository. Participation in the repository will be completely voluntary and entirely optional which means that a potential participant's willingness to participate in the repository has no influence upon their eligibility to participate in the primary STRONG STAR study they have either already enrolled in or are considering enrolling in. At the conclusion of this study, participants who signed the consent to have their specimens and data placed in the STRONG STAR Repository will be maintained under the IRB-approved Repository protocol. Biological specimens and information from study participants who declined participation in the STRONG STAR Repository will be permanently de-identified (i. e., all PHI will be deleted from the study data bases) and the de-identified blood and information placed in the STRONG STAR Repository for future use.

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11.0 TIME REQUIRED TO COMPLETE THE RESEARCH (including data analysis). 48 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 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.

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Appendices:

A- Consent to Contact
B- Telephone and In-Person Script and Pre-Screen Questionnaire
C- Data and Safety Monitoring Plan

D- Recruitment Flyers