HUMAN SUBJECTS RESEARCH PROTOCOL

1. PROTOCOL TITLE: Safety, feasibility, and benefits of transcranial direct current stimulation (tDCS) in human subjects with PTSD receiving an exposure-based, behavioral therapy

2. ABSTRACT.

Symptoms of posttraumatic stress disorder (PTSD) include intrusive memories about the event, physiological hyperarousal, sleep difficulties, and negative alterations to mood and cognitions, all of which can have significant, long-term effects on health and functioning. Evidence-based non-pharmacological, psychotherapies for PTSD exist and are well-established (Lewis et al., 2020). However, there remains room for improvement in outcomes given that a proportion of patients (~50%) do not significantly benefit from treatment (Steenkamp et al., 2015a). The field of non-invasive brain stimulation is rapidly gaining considerable attention as a potential therapeutic for PTSD based on the ability to modulate brain activity in regions associated with the fear response and extinction learning (two critical constructs associated with PTSD pathology and PTSD treatment). While the potential for non-invasive brain stimulation is exciting, research is needed to determine the safety, feasibility, and benefits of non-invasive brain stimulation in human subjects with PTSD. Towards this end, we will conduct a partially double - blind randomized controlled pilot study of transcranial direct current stimulation (tDCS) vs. a sham condition in a sample of 40 adults with PTSD receiving 5 weekly sessions of Written Exposure Therapy (WET), an exposure-based, behavioral psychotherapy for PTSD.

3. OBJECTIVES/SPECIFIC AIMS/RESEARCH QUESTIONS.

The primary objective of this study is to evaluate the safety, feasibility, and psychological and physiological treatment benefits of tDCS, a noninvasive brain stimulation technique, when delivered in combination with WET for PTSD.

Specific Aims and Hypotheses:

Aim 1: To evaluate the safety of tDCS vs. sham when combined with WET.

Hypothesis 1: tDCS can be safely combined with WET for PTSD as indicated by minimal adverse events (AEs) and high tolerability of any observed study related AEs.

Aim 2: To evaluate the feasibility of combining tDCS with WET for PTSD as measured by rates of enrollment, recruitment, and treatment completion.

Aim 3: To explore PTSD symptom reductions associated with tDCS vs. sham when combined with WET.

Hypothesis 2: tDCS can reduce PTSD severity more so than a sham condition when combined with WET for PTSD on the PTSD Checklist (PCL-5).

Hypothesis 3*:* tDCS can decrease physiological arousal (heart rate and galvanic skin response) associated with the stress response during written exposure.

4. MILITARY RELEVANCE.

The proposed study will recruit civilians and military veterans seeking PTSD treatment. Although this study will recruit a mixed sample of civilians and veterans, findings from this study can inform existing literature focused on military-related PTSD. Compared to civilians, the rate of PTSD is particularly elevated among military populations, with approximately 23% of military vs. 6-8% of civilians meeting criteria for PTSD (Fulton et al., 2015). Furthermore, PTSD has been identified as the signature deployment-related psychiatric condition among service members. The functional impact of PTSD can cost service members their military careers and veterans with PTSD are at increased risk of unemployment and homelessness following military separation (Asnaani et al., 2014). Notwithstanding evidence that current first-line treatments are effective for PTSD, there remains room for improvement in outcomes given that a large proportion of patients (~50%) do not significantly benefit from treatment (Steenkamp et al., 2015b). Research dedicated to evaluating novel treatments for PTSD has the potential to promote greater PTSD treatment efficacy that will lead to greater symptom reductions, positive well-being, and improved functioning in the military community.

5. BACKGROUND AND SIGNIFICANCE.

Impact and Prevalence of PTSD: Approximately, 70% of the U.S. population (~232 million) will experience a traumatic event in their lifetime and 7% of those individuals (~16 million) will go on to develop PTSD (Benjet et al., 2016). Symptoms of PTSD can include fear, anxiety, negative mood, uncontrollable/negative thoughts about the event, sleep disturbances, and avoidance of environmental trauma reminders. The impact of PTSD is substantial and often results in chronic,

pervasive functional problems with relationships, work, and physical health (Asnaani et al., 2014). When left untreated, it can lead to detriments in mental health and psychosocial functioning (Pacella et al., 2013; Thomas et al., 2010). The overall impact of PTSD is substantial and often leads to significant burdens on the individual, their family, and the community (Renshaw et al., 2011). The sequalae of PTSD not only impacts an individual's immediate environment but also places significant burden on society due to increased work sick days and greater healthcare utilization (Asnaani et al., 2014; Thomas et al., 2010).

Non-Pharmacological, Psychotherapy Approaches to PTSD Treatment: Evidence-based non-pharmacological, psychotherapies for PTSD exist and are well-established (Lewis et al., 2020). Written Exposure Therapy (WET) is a type of first-line, exposure-based psychotherapy for PTSD that is recommended in the International Society for Traumatic Stress Studies (ISTSS) and Veterans Administration and Department of Defense (VA/DoD) Clinical Practice Guidelines (Forbes et al., 2020; VA/DoD, 2018). WET aims to reduce trauma-related distress and PTSD symptoms through an exposure-based intervention that promotes extinction learning and emotional processing by writing about the traumatic event (Sloan et al., 2018, 2020; Sloan & Marx, 2019). Extinction learning can be defined within the context of operant and classical conditioning theory, where there is a gradual decrease in response that occurs when a stimulus is presented without reinforcement. Exposure to a traumatic event and PTSD can result in the development of a maladaptive fear response. That is, an individual's response to "innocuous," conditioned stimuli (e.g., "a crowded restaurant") can be repeatedly interpreted as "dangerous" (i.e., conditioned response) based on the prior exposure to a traumatic event (e.g., "bomb exploded in a crowded area while deployed to a combat zone"). This interpretation often prompts negative reinforcement behaviors (i.e., avoidance or safety strategies to reduce anxiety) that prevent extinction learning processes to the feared conditioned stimuli (Foa et al., 1991). During WET, individuals are encouraged to approach the trauma memory through writing about the event so that they can make sense of the trauma, develop healthy coping strategies, and mitigate avoidance behaviors. WET is comprised of five treatment sessions and is a brief, scalable first-line psychotherapy for PTSD. During each WET session, patients write about their traumatic event using empirically supported, therapist-guided writing instructions for approximately 30 minutes. In the first session, the therapist guides the participant through the writing. In subsequent sessions, participants complete writing independently. Individuals are prompted to write about the details of the traumatic event during initial writing sessions and then about the impact of the trauma in later sessions. Following the half hour of writing, the therapist briefly meets with the participant for 15-30 minutes to talk about their writing. At the end of the appointment, individuals are encouraged to allow themselves to think about the trauma between session, but no formal between session homework assignments are assigned. Overall, research has shown that WET is non-inferior to CPT, a first-line psychotherapy for PTSD and requires less than half of the sessions (Sloan et al., 2018). Notwithstanding evidence that WET and other first-line psychotherapies are effective treatments for PTSD, there remains room for improvement in outcomes given that a large proportion of patients (~50%) do not significantly benefit from treatment (Steenkamp et al., 2015). Overall, the therapeutic needs of individuals with PTSD are significant and combined interventions that adapt currently available treatments have the potential to improve outcomes for many individuals suffering from PTSD.

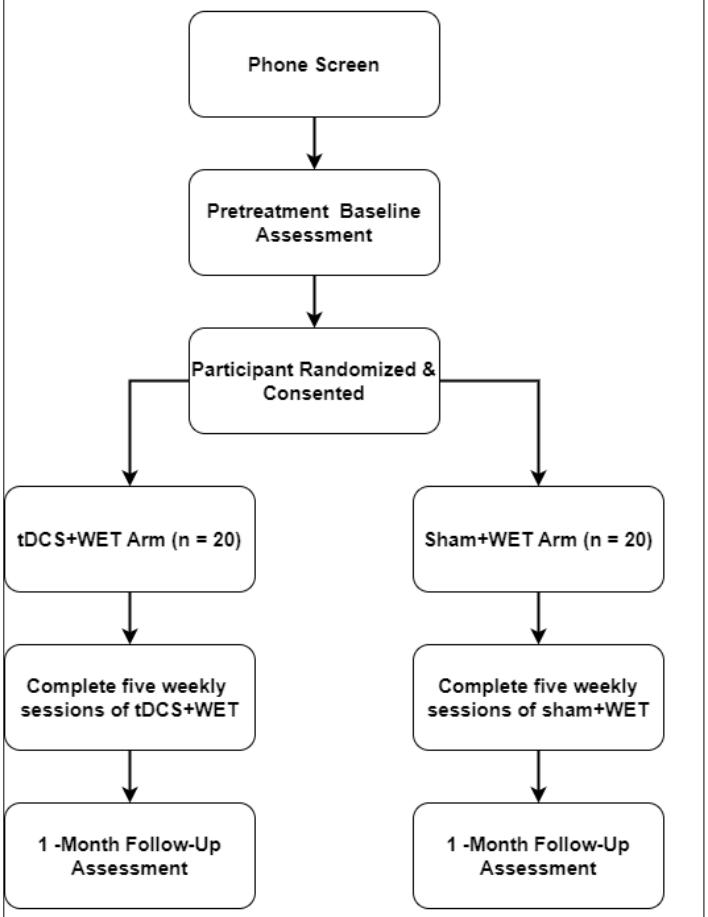
PTSD and the Brain: As noted above, the constellation of PTSD symptoms is largely characterized by a maladaptive fear response. First-line psychotherapies for PTSD aim to target and modify the individual's fear response through extinction learning interventions. Therefore, the success of exposure-based psychotherapy is dependent on the efficacy of extinction learning. Within the brain, the fear response and conditioned learning are associated with the prefrontal cortex (PFC), which modulates fear signaling (i.e., extinction learning) between the amygdala and dorsal anterior cingulate. Research has shown that PFC signal modulation to other critical brain areas is associated with extinction learning. These pathways are often inhibited for individuals with PTSD (Etkin & Wager, 2007). Therefore, interventions that can augment activity in brain areas related to extinction learning, particularly during an exposure-based task, are of high relevance for PTSD treatments.

Transcranial Direct Current Stimulation (tDCS): One promising method to activate brain regions critical to extinction learning is non-invasive brain stimulation, which permits targeted intervention of the aforementioned brain regions associated with PTSD. Non-invasive brain stimulation was first performed over 80 years ago when Ugo Cerletti and his collaborators used electricity to induce seizures in a patient with paranoid psychosis. Electroconvulsive therapy (ECT) continues to be in use today; however, while effective, the risk of adverse cognitive effects limits the use of ECT to severe, treatment-resistant patients. More recently, there have been advances in non-invasive brain stimulation techniques that are safer and do not result in the negative side effects associated with ECT. Specifically, the use of repetitive transcranial magnetic stimulation (rTMS) and tDCS have provided a significant advance whereby pathophysiological alterations in the brain can be safety targeted without significant negative side effects (Clark et al., 2015; Marin et al., 2014; van 't Wout-

Frank et al., 2019; van 't Wout et al., 2017). tDCS is of particular interest because of its cost-effectiveness, device portability, and robust safety/side effect profile (Bikson et al., 2016). tDCS involves the use of a low grade (subthreshold), consistent electrical current (1-2 mA) that is typically delivered through two electrodes placed on the scalp for approximately 30 minutes (Nitsche et al., 2008). During stimulation, a current flows between the electrodes passing through the brain to complete the circuit. tDCS is hypothesized to modulate intrinsic neuronal activity by enhancing neuronal resting potential, or altering the likelihood that a neuron will (or will not) depolarize (Rahman et al., 2017). Anodal tDCS increases the excitability of the cortex whereas cathodal tDCS decreases it.

Safety and Effect of tDCS: There has been a great deal of research on the safety of tDCS, which suggests that the technique is safe, does not cause permanent or severe damage, or discomfort when used according to appropriate guidelines (Thair et al., 2017). To date, the use of conventional tDCS protocols in human trials (≤40 min, ≤4 mA) has not produced any reports of Serious AEs or irreversible injury across over 33,000 sessions and 1,000 subjects with repeated sessions (e.g., Bikson et al., 2016). These results comprise a diverse pool of subjects that includes individuals from potentially vulnerable populations (e.g., those with a psychiatric diagnosis, in pain, and those with neurological conditions). Overall, tDCS has received a "nonsignificant risk" determination from different IRBs monitoring a number of trials (Fregni et al., 2015). Typical side effects are minor and transient (e.g., skin irritation, tingling, and minor headaches), with such AEs mitigated by appropriate screening (e.g., exclusion for history of skin condition) and the use recommended tDCS guidelines (Bikson et al., 2016; DaSilva et al., 2011; Thair et al., 2017).

Figure 1. Study Design Overview



Notes. Participants will also complete 5 interim assessments prior to each session and wear GSR and HR monitoring devices during sessions 1, 3, and 5. Detailed study procedures are described in Section 7.3

Existing research on the effects of tDCS for a variety of psychiatric conditions is promising but remains in the early stages of exploration (see Kekic et al., 2016). Depression is the most extensively researched use of tDCS to treat psychiatric conditions to date, but preliminary studies have also evaluated conditions, such as schizophrenia, substance use, and anxiety-related disorders. With regard to PTSD, preliminary, proof-of-concept laboratory models in humans have demonstrated that non-invasive brain stimulation via tDCS can stimulate the PFC and reduce maladaptive fear responses during an extinction learning task, with minimal AEs that are highly tolerable (Raij et al., 2018;van 't Wout et al., 2016; van 't Wout et al., 2017). In a pilot study of tDCS vs. sham combined with a virtual reality exposure protocol, a sample of military veterans demonstrated a reduction in physiological and self-reported PTSD symptoms, with minimal AEs (van 't Wout-Frank et al., 2019). Current tDCS approaches for PTSD appears promising, but more research is needed. As detailed above, the PFC plays a central role in several processes altered in PTSD. Prefrontal hypoactivity has been consistently reported in patients with PTSD. Given that anodal tDCS stimulation is postulated to produce neuronal activation, whereas cathodal tDCS induces hyperpolarization, anodal tDCS may reverse the PFC hypofunction seen in PTSD patients. Overall, tDCS represents a novel and conceptually informed method to improve PTSD treatment outcomes, especially if paired with an exposure-based psychotherapy.

6. RESEARCH DESIGN.

This study is an early phase II, two-arm, partially double-blind pilot RCT to explore the safety, feasibility, and effects of tDCS vs. sham delivered in combination with WET among individuals seeking treatment for PTSD. As seen in Figure 1, all individuals will complete a phone screen to learn more about the study to include the inclusion and exclusion criteria. Study candidates will be recruited from the University of Texas Health Science Center at San Antonio (UTHSCSA)

Psychiatry Outpatient Clinics, and the San Antonio community. Participants will be recruited from the South Texas Veterans Healthcare System (SVTHCS) by responding to flyers approved and posted by Public Affairs. Interested participants who appear to meet eligibility criteria will be consented and then complete a baseline assessment to determine study eligibility. Eligible participants will be randomized to five weekly sessions of tDCS, or sham, combined with WET for PTSD. tDCS (or sham) will be simultaneously delivered during the writing exposure portion of WET for 30 minutes each session. Outcomes to address study objectives will include (1) safety as measured by the adverse events (AE) monitoring logs, (2) feasibility based on *study recruitment* (number of contacted referrals who were eligible to begin the full baseline assessment over the total number of contacted referrals [will not to include non-contact referrals]), *screening* (number screened eligible following baseline assessment over the total number of individuals who completed a baseline assessment), and *treatment completion* (number who completed all 5 sessions over total randomized), and (3) the associated effects of tDCS for PTSD as measured by the PCL-5 and physiological stress response (as measured by heart rate and galvanic skin response). Assessments will be collected twice to satisfy study aims at baseline and one-month follow-up. Select measures will also be administered during treatment (Table in section 7.3).

6.1.1. Randomization. This study will use a partially double-blind randomization design. All participants will be blinded to treatment arm. With the exception of one non-clinical, research team member, all other members of the research team will also be blinded to treatment arm. This approach is so that the PI and research team can be quickly made aware of which treatment arm the participant is assigned to in the event of an emergency.

7. RESEARCH PLAN.

7.1.1. Subject Population. Participants will be individuals 18-65 years old who meet diagnostic criteria for PTSD on the Clinician Administered PTSD Scale (CAPS-5). Efforts will be tailored to equally recruit diverse individuals across sex, gender/sexual orientation, race, age, disability, socioeconomic status, national origin, and branch of military service.

7.1.2. Inclusion and Exclusion Criteria.

Inclusion Criteria

1. Individuals between the ages of 18 and 65 years old at time of screening.
2. PTSD diagnosis as assessed by the Clinician-Administered Posttraumatic Stress Scale (CAPS-5)
3. Able to write, read, and speak English.

Exclusion Criteria

1. History of epilepsy or seizures.
2. History of significant intracranial pathology (e.g., severe traumatic brain injury) or neurological disorder (e.g., Stroke, Multiple Sclerosis, Amyotrophic Lateral Sclerosis, Alzheimer's, Dementia, Parkinson's, and/or Huntington's).
3. History of skin condition (e.g., eczema, psoriasis) where electrodes will be applied.
4. Electronic implants in the body that could be susceptible to electrical current (e.g., cardiac pacemaker, cochlear implants, medical pump).
5. Metallic objects other than dental appliances/fillings near the site of stimulation
6. Current manic episode or psychotic symptoms requiring immediate stabilization or hospitalization (as determined by clinical judgement).
7. Current moderate or severe substance use disorder.
8. Suicidality and/or psychiatric risk requiring immediate intervention or a higher level of care than can be provided by the study treatment.
9. Change in anticonvulsive or benzodiazepine medication regimen in the past month.
10. History of adverse effects to previous tDCS or other brain stimulation technique.
11. Concurrent engagement in another brain simulation technique or trauma-related psychotherapy for PTSD.
12. Currently pregnant or breastfeeding.

7.1.3. Description of the Recruitment and Prescreening Process. Participants will be recruited through the UTHSCSA Outpatient Psychiatry Clinics located on the 7th Floor of the Medical Building and University Park Plaza (i.e., Advance Clinic, Be Well Clinic, Transitional Care Clinic), and the San Antonio community through provider referrals, recruitment events, and flyers. Participants will be recruited from the South Texas Veterans Healthcare System (SVTHCS) by responding to flyers approved and posted by Public Affairs. Providers can give their patients contact information for the study staff so that interested individuals may contact STRONG STAR directly. Alternatively, providers can obtain consent-to-contact from their

patients that allows the study staff to contact the potential participant directly. Co-Investigator, Melissa Martinez, MD, a psychiatrist, Professor, and the Director of the Interventional Psychiatry Program at UTHSCSA, which offers brain stimulation interventions for patients with PTSD and other psychiatric diagnoses, will also refer participants for the study. Individuals who are not eligible or interested in other IRB-approved STRONG STAR protocols will be told about this study. Study information will be posted on the STRONG STAR website and social media. Patients can self-refer themselves to the study. Under an IRB-approved HIPAA Waiver of Authorization, study personnel will initially conduct a brief telephone interview where the basic study inclusion/exclusion criteria will be reviewed. This will mitigate unnecessary travel and more in-depth screening for individuals. Participants who appear eligible after telephone pre-screening will be invited into the STRONG STAR clinic to provide written informed consent and undergo more rigorous assessment for study eligibility.

7.1.4. Consent Process. During the consent appointment, potential participants will have the study explained to them in a private location in-person at the UTHSCSA STRONG STAR offices located at 7550 IH10 West, Suite 1325, San Antonio, TX 78229. The potential participant will be given a copy of the informed consent document (ICD) to read. After the potential participant has read the ICD, and a member of the study team has reviewed the risks and benefits of the study to ensure the participant understands the research, the participant will be given the opportunity to 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 participant will sign the consent form. A copy of the signed ICD will be given to the participant.

7.1.5. Subject Screening Procedures. Following consent, a baseline assessment will take place to determine participant eligibility. The entire screening process will take approximately 4 hours. This will include the completion of the questionnaires, interviews, and screening tests outlined in the Table of Assessments below (see section 7.3). The baseline assessment 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 undergone baseline testing 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 baseline testing 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.

7.1.6. Source of Research Material. All measures will be administered for research purposes. For a complete list of measures see Section 7.3.

7.1.7. Compensation for participation. Participants will be paid $25 for physiological assessment of Heart Rate and Galvanic Skin Response at sessions 1, 3, and 5 for a total of up to $75. 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.

7.2 Study Device Overview. Transcranial Direct Current Stimulation (tDCS) will be the active intervention for this study. tDCS will be administered using a Soterix 1x1 Transcranial Direct Current Stimulator Mini-Clinical Trials (Model 1601) and two 5cm x 7cm Soterix SNAPpad electrode sponges soaked in saline solution that are secured to the head with the Soterix SNAPstrap. SNAPpad sponges have a pre-inserted carbon rubber snap electrode that connects directly to the designated electrode montage site on the SNAPstrap. The SNAPstrap is a customized head-gear strap positioned to target the designated tDCS area. The SNAPstrap includes fixed electrode sites and built-in cabling for simple and consistent device set-up. Soterix is an established, reputable medical brand that provides medical grade quality transcranial electrical stimulation devices. The Soterix 1x1 includes programmable intensity (2.0mA) and duration (30 min) features so that each stimulation session is standardized, as well as contact quality monitoring to ensure the electrodes are secured prior to and during the session. The device includes a sham condition setting to enable a matched tDCS sham waveform that allows for flexibility in testing in a research study. The device also has an abort option, which will terminate the session and ramp down the device, as necessary.

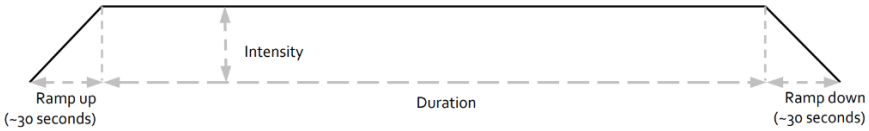
Medical devices, such as tDCS, are regulated by the FDA regardless of indications for use. We are requesting that the IRB consider an "Investigational Device Exception (IDE)" for tDCS. See completed Form P, "Use of an IDE in Research." Based on other studies conducted in the US, the IRBs have designated tDCS to be of nonsignificant risk (see Fregni et al., 2015). We are not seeking a new indication for tDCS with the data from this research project.

7.3. Study Procedures/Research Interventions. The intervention to be tested in this study is *Transcranial Direct Current Stimulation (tDCS).* tDCS procedures and dose for this study will be consistent with conventional published clinical practice guidelines (≤40 min, ≤4 mA; Bikson et al., 2016) and will be delivered in combination with Written Exposure Therapy (WET), an evidence-based, trauma-focused psychotherapy for PTSD (Sloan & Marx, 2019).

For this study, individuals will complete the following procedures at each session.

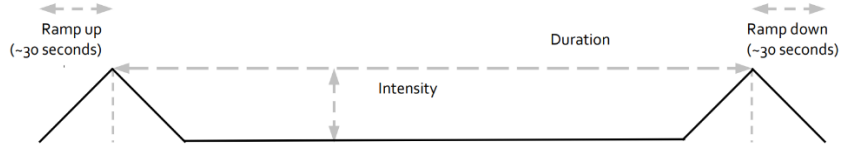
- Upon arrival, participants will complete self-report measures prior to their session as described in Table 7.3.
- Consistent with the WET protocol, session 1 will be 90-minutes while sessions 2-5 will be 60-minutes. All sessions will include a 30-minute intervention of tDCS (or sham) plus written narrative followed by approximately 15-30 minutes to review writing with a study therapist. Session 1 includes psychoeducation on PTSD and review the treatment rationale (approximately 30-45 minutes) at the beginning of the session (prior to the writing), while subsequent sessions (2-5) begin with the writing.
- The tDCS (or sham) intervention will be delivered during the written narrative portion of each session. A trained study team member will prepare the participant for tDCS after review of psychoeducation/rationale in session 1 and prior to sessions 2-5. Two electrodes in saline-soaked sponges (SNAPpads) will be placed on the participant scalp. The anode will be placed over the left dorsolateral prefrontal cortex (lDLPFC) while the cathode will be placed over the right dorsolateral prefrontal cortex (rDLPFC), consistent with previous work (Ahmadizadeh et al., 2019). The electrodes will be secured to the head using customized straps (SNAPstraps) designated to target the desired brain regions. As described in Section 7.2, electrode and strap procedures will be completed using standardized, preset equipment to maximize efficiency and reproducibility of positioning.
- Next, the study team member will place the HR and GSR device on the individual's non-writing hand and begin monitoring. The participant will then begin the writing exposure and tDCS device will be activated. The Soterix device has standardized programming so that all participants receive the same dose (or sham) and intervention based on the set procedures. The tDCS device will be set at 2.0mA for a total of 30-minutes. Once the "start" button is clicked by the study team member, the device is programmed to gradually ramp up current to the set intensity dose (2.0mA in this study) in the first 30-seconds. As seen in Figure 1, in the active intervention the current will remain at 2.0mA for 30-minutes and then the programmed device will gradually ramp down from 2.0mA to 0.0mA in the final 30-seconds.

Figure 1. tDCS active condition



As seen in Figure 2, during sham stimulation, participants will experience the gradual current ramp up from 0.0 mA to 2.0mA in the first 30-seconds and then a gradual ramp down from 2.0mA to 0.0mA (30-seconds). The programmed device will automatically repeat this process at the end of the set duration of 30 minutes.

Figure 2. tDCS sham condition



A study team member will be in the immediate proximity during tDCS (or sham)/written exposure to monitor participant safety and abort the tDCS, if necessary. Clicking the "abort" button will initiate a ramp down of current to 0.0mA. A medical provider will also be available should the participant experience a serious AE or require a higher level of medical care.

- Following the tDCS (or sham) and writing, a study team member will remove the tDCS and HR/GSR device. Consistent with WET, the participant will meet with a study therapist to review their writing for 15-30 minutes. During this time, the participant will also be monitored for safety prior to leaving the appointment.

7.3.1 Collection of Human Biological Specimens. Females will complete a CLIA-waived hCG pregnancy test at baseline for screening eligibility purposes.

7.3.2 Data Collection. See Table in Section 7.3 for a summary of the assessments and timing of administration. The data collected in the study will be coded using an assigned number. Hard copies of data collected during the study will be securely stored in locked cabinets at the STRONG STAR offices. Data will be entered into the STRONG STAR database by a member of the research team.

7.3.2.1 Instrumentation. See the table in Section 7.3 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, 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, video conferencing, and/or electronic data capture using a secure link to the encrypted STRONG STAR database. 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.

Visit/Assessment/Follow Up (F/U) Interval							
Study Day	**Pre/BL**	**S1**	**S2**	**S3**	**S4**	**S5**	**Post**
Informed Consent	R						
Interventions							
tDCS/Sham		R	R	R	R	R	
WET		R	R	R	R	R	
Clinical Interviews							
1. Clinician Administer PTSD Scale-5 (CAPS-5)	S,R						R
2. STRONG STAR Health Questionnaire	S,R						R
3. Health Questionnaire Addendum for tDCS	S,R						
4. Self-Injurious Thoughts and Behaviors Interview (SITBI)	S,R						R
Self-Report Questionnaires							
5. PTSD Checklist-5 (PCL-5)	R	R	R	R	R	R	R
6. Patient Health Questionnaire-9 (PHQ)	S,R	R	R	R	R	R	R
7. Generalize Anxiety Disorder-7 (GAD)	R	R	R	R	R	R	R
8. Posttraumatic Cognitions Inventory (PTCI)	R	R	R	R	R	R	R
9. Depressive Symptom Index-Suicidality Subscale (DSI-SS)	S,R	R	R	R	R	R	R
10. Adverse Events Monitoring		R	R	R	R	R	R
11. tDCS Reaction Monitoring		R	R	R	R	R	
12. Demographics Questionnaire	S,R						
13. Life Event Checklist-5 (LEC)	R						R
14. Brief Inventory of Psychosocial Functioning (B-IPF)	R						R
15. Quick Drinking Screen (QDS)	R						R
16. Drug Abuse Screening Test (DAST)	S						
17. Insomnia Severity Index (ISI)	R						R
18. Cognitive Emotions Regulation Questionnaire (CERQ)	R						R
19. History of Head Injuries	R						
20. Neurobehavioral Symptom Inventory	R						R
21. Numeric Rating Scale for Pain Intensity	R						R
22. PROMIS Pain Interference Short Form 8a	R						R
23. Credibility and Expectancy Questionnaire for WET (CEQ)			R				
24. Credibility and Expectancy Questionnaire for tDCS (CEQ)			R				
Physiological/Biological Measures							
25. Heart Rate		R		R		R	
26. Galvanic Skin Response		R		R		R	
27. hCG Pregnancy Test*	S						
Notes. S=Screening Purposes, R=Research Purposes; Pre/BL= Baseline Assessment, S=session, Post = one-month post-treatment follow-up; Heart Rate and Galvanic Skin Response measurement will occur during the writing portion of sessions 1, 3, and 5, using Fitbit wrist watch; *Females only.							

7.3.2.2 Data Storage, Access and Protection. Study files containing hard copies of data collected during study participation will be kept securely at the STRONG STAR offices in San Antonio. Files will be placed into locked cabinets and stored securely in a locked room by a STRONG STAR staff member. Data will be coded using an assigned number. Local study sites will maintain a list of assignment numbers for the purpose of linking subsequent research materials. Data will be entered into the STRONG STAR password protected database housed on a secure UTHSCSA server by member of the research team. Electronic data will be stored, managed, and analyzed by the STRONG STAR Data and Statistics Services staff of the STRONG STAR consortium. The overall PI and named collaborators will have access to identifiable data through the STRONG STAR website and UTHSCSA server via direct request to STRONG STAR Data and Statistics Services.

All UTHSCSA STRONG STAR network connectivity is segmented with Access Control Lists and is not accessible to any other UTHSCSA network segments. The STRONG STAR data server is physically located at the Advanced Data Center (ADC), which has 24x7 onsite security, card key, biometric access controls and video surveillance. 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. The UTHSCSA STRONG STAR data server is currently a VMware Instance running Windows Server 2018 Enterprise Standard with daily backup services and vSphere Business Continuity Advanced Failover.

Only select STRONG STAR Data and Statistics Services personnel have direct access to the data on a "need to access basis"; for example (but not limited to) detecting and repairing data corruption and producing reports not currently within the STRONG STAR system. STRONG STAR Data and Statistics Services also follows the Principals of Least Privilege (POLP). All user activity is tracked and recorded within the system so if any records are added, altered, or viewed the action is recorded and can be recalled for auditing purposes. Access to this information will require a password-protected login available only to authorized STRONG STAR Data and Statistics Services staff.

Every member of the Research Team will be trained and monitored about how to handle and protect both research records. Furthermore, the Research Team strictly controls access to study data. The STRONG STAR Data Safety and Monitoring Plan (DSMP) that has been developed in accordance with the National Institutes of Health Office of Human Research Protection to assure the appropriate clinical safety monitoring of study subjects participating in research will be used to monitor this study.

7.4 Statistical Consideration

7.4.1 Sample Size Estimation.

Total Required to Consent	**50**
Estimated Participant Screen Fail / Exclusion (20%)	**10**
Target Sample Size to be Randomized	**40**
Estimated Participant Drop Out / Withdrawal after randomization (15%)	**6**
Expected Treatment Completers	**34**

7.4.2 Primary (i.e., primary outcome variables) and secondary endpoints (See Table in section 7.3). *Adverse event (AE) monitoring* will address study Aim 1. To assess study feasibility (Aim 2), we will track study recruitment (number of eligible referrals/total referrals), enrollment (number of screened enrolled participants/total eligible), and treatment (number of participants who completed all 5 WET sessions). *The PCL-5* (Weathers, Litz, et al., 2013) will be the primary outcome to assess PTSD severity (Aim 3a). *Heart rate (HR)* and *galvanic skin response (GSR)* will be used to address Aim 3b.

7.4.3 Data analysis.
Power Analyses: This pilot study is not powered for formal efficacy or mechanistic hypotheses testing. Consistent with research regarding the purpose of a pilot study, our main interests were to evaluate the feasibility of the proposed recruitment, assessment, and treatment protocols, examine safety, and to explore a detectable effect of tDCS across outcomes in preparation for a larger trial (Kraemer et al., 2006; Leon et al., 2011). Although the statistical power of this study is limited, we will perform statistical analyses appropriate for an adequately powered study to identify data analysis issues germane to future planning.

Data Analyses: Prior to developing statistical models, all variable distributions will be examined using frequency distributions, scatter plots, and histograms. Statistics such as means or proportions, standard errors, ranges, and estimates of skewness and kurtosis will be computed and used as guidelines in the application of analyses. Data transformation procedures may be applied to variables with considerable departure from normality.

The objectives of this study are to evaluate the safety, feasibility, and PTSD symptom reductions associated with tDCS vs. sham. All statistical analyses will be intent to treat and include all participants randomized at baseline regardless of the

extent of study participation. Given the small sample size, we will use a Benjamini-Hochberg Adjustment procedure to mitigate the false discovery rate (two tailed initial p = .05). Analyses will be done SPSS 27 statistical software. As needed, we also have access to SAS 9.4, Stata 14.2, R, and Mplus 8.4 software.

Descriptive Statistics to Address Aims 1 and 2: Descriptive statistics will be used to address the safety and feasibility of tDCS when combined with WET. To assess, safety, we will evaluate the frequency, severity, and relatedness of AE based on the STRONG STAR AE monitoring procedures. AE logs will be reviewed and adjudicated with the study team during weekly meetings to evaluate reliable coding and participant safety. Casey Straud, PsyD (PI) and Melissa Martinez (Co-I; Attending Physician) will also hold one-on-one meetings as needed to mitigate health related AEs and monitor participants. To assess study feasibility, we will estimate recruitment (number of eligible referrals/total referrals), enrollment (number of screened enrolled participants/total eligible), and treatment (number of participants who completed all 5 WET sessions). Feasibility data will be used to inform planning for a larger clinical trial.

Generalized Linear Mixed Models (GLMM) to Address Aim 3: GLMM will be used to evaluate changes in continuous outcomes associated with tDCS vs. sham. GLMMs are a powerful and flexible statistical extension of linear mixed models that can examine outcome variables from different distributions, such as normal (continuous) and binary outcomes. Advantages of likelihood-based regression models over conventional ANOVA include the ability to use data from all participants even if they have only baseline data, relaxation of the assumption of equal variances before and after treatment, specification of data distributions other than normal such as Poisson or log-normal, and the ability to analyze longitudinal data in the presence of missing data given the assumption that data are missing at random. GLMM's will include fixed effects of time, treatment (tDCS vs. sham), and the time by treatment interaction. Models will include *a priori* planned contrasts of mean differences over time and simple effects to evaluate treatment differences at each time point. To inform future studies, we will calculate conventional effect sizes with 95% confidence interval limits (Hertzog, 2008). Hedges' *g* will be used to calculate continuous outcome effect sizes (e.g., PCL-5). Hedges' *g* has been recommended over Cohen's *d* for small samples based on sample size adjustments, yet can be interpreted using the same conventional recommendations as Cohen's *d,* .20 =small, .50=medium, and .80=large effect sizes (Lakens, 2013).

Assessment timepoints are presented in the 7.3 Table. The PCL-5 will be the primary outcome to evaluate changes in PTSD severity from baseline assessment to one-month follow-up, with data points collected during treatment also included in models (Aim 3a). Heart rate monitoring and GSR will be used to evaluate physiological stress arousal during the writing exposure task (Aim 3b). Both physiological outcomes will be collected during the writing exposure portion of sessions 1, 3, and 5 to provide before, after, and peak estimates of physiological arousal. Time points of interest for physiological outcomes will be the *immediate*, *long-term, and peak* effects of tDCS. The *immediate* effect of tDCS will be defined as changes immediately prior to and after the first written exposure (i.e., change from T_1 to T_2), the third written exposure (change from T_3 to T_4), and the last time participants engage in writing exposure (change from T_5 to T_6). The *long-term* effect of tDCS will be defined as changes in physiological levels across sessions (session 1 to session 5) prior to engaging in the writing exposure (change from T_1 to T_5) and after the writing exposure (change from T_2 to T_6). The *peak* effect will evaluate change score differences (interaction effect) in the greatest estimate during session 1 to session 5.

7.5 Confidentiality. Pretreatment (baseline) and posttreatment (one-month follow-up) assessments will be primarily delivered in private offices at the STRONG STAR clinic at the UTHSCSA located at 7550 IH10 West, Suite 1325 in San Antonio, TX. tDCS or sham + WET sessions will be delivered in private offices at the STRONG STAR clinic. All treatment sessions will be completed in person. When travel to the STRONG STAR clinic is not feasible for the one-month follow-up assessment, video teleconferencing will be made available to mitigate missed appointments. Data will be stored by an assigned participant code number so that data records can be viewed by password-authenticated, authorized investigators and Consortium personnel. Digital audio recordings of assessments will be labeled with the participant's study id number and saved on a secure password protected server. Those recordings may be reviewed for adjudication on PTSD diagnosis or to ensure that the assessment was delivered in accordance with training guidelines. Any assessment recordings will be viewed on a secure password protected server. There is no option for the reviewers to download or otherwise save the recordings to their computers. Every member of the research study team will be trained and monitored on how to handle and protect both medical and research records. Only authorized study staff, and members of the STRONG STAR Data and Statistics Services staff will have access to either the raw data or electronic study data. We are not seeking a Certificate of Confidentiality.

7.7.3. Long Term Data Storage. A *STRONG STAR Repository* has been approved by the UTHSCSA (HSC20100475H) IRB to enable the STRONG STAR Consortium to store specimens and data for future use. The *STRONG STAR Repository* is a

large comprehensive database of information, biological specimens and neuroimages related to the identification, assessment, and treatment of posttraumatic stress disorder (PTSD), insomnia, pain, and related behavioral health conditions. 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 in collaboration with the UTHSCSA STRONG STAR Consortium. Study databases are established and maintained by the Data Management and Biostatistics 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 Data Management and Biostatistics Core. At the conclusion of this study, participants who signed the consent to have their data placed in the *STRONG STAR Repository* will be maintained under the UTHSCSA IRB-approved Repository protocol. For participants who decline participation in the *STRONG STAR Repository*, at the conclusion of the study their data will be de-identified and the data maintained in the Repository without identifiers.

8.0 RISKS/BENEFITS ASSESSMENT

8.1 Risks. tDCS and WET are safe and well tolerated by human subjects, but are associated with minor, transient adverse effects. In human trials to date, the use of tDCS within the recommended clinical guidelines (≤40 min, ≤4 mA) has not produced any reports of a Serious Adverse Effect or irreversible injury across over 33,200 sessions and 1,000 subjects with repeated sessions. However, like many medical devices, AEs are possible. tDCS risk information presented below is aggregated from the following references (Ahmadizadeh et al., 2019; Bikson et al., 2016; DaSilva et al., 2011; Davis & Smith, 2019; Fregni et al., 2015; Thair et al., 2017). PTSD and WET risk information presented below is from the International Society for Traumatic Stress Studies (ISTSS) clinical practice guidelines (Forbes et al., 2020)

Likely, but Not Serious Risks (expected to occur in 15-30 out of 100 participants):

tDCS: The most common adverse effect of tDCS include mild itching sensation at the point of contact with the electrodes. These AEs can be mitigated by excluding individuals with a history of skin condition, the use of saline solution, and limiting the intervention to 40 min or less with ~1-week in-between sessions.

WET: Temporary increases in psychological distress can occur among individuals engaged in WET for PTSD.

Less Likely, some may be Serious (expected to occur in 10-18 out of 100 participants):

tDCS: Transient minor discomfort can occur in about 10-18% of participants, such as mild headaches, nausea, mild burning sensation at the point of electrode contact, and fatigue. However, the relatedness of AEs to tDCS remains unclear as many controlled trials have demonstrated no difference between the tDCS and sham conditions.

Rare and Serious (expected to occur in <1 out of 100 participants):

tDCS: A rare but serious AE of tDCS can be skin lesions following repeated tDCS. As noted above, the risk of both skin lesions and itching/burning sensations can be minimized by soaking the connecting sponges in sodium chloride (saline) solution rather than water before commencement of stimulation. Another potentially serious AE that has been discussed in the literature is seizures. To date, there is no documented evidence that tDCS has resulted in a seizure and this may be explained by the subthreshold current used in tDCS. However, there is a theoretical rationale that brain stimulation can increase the risk of seizures.

Risks to Confidentiality: With the handling of medical and research records there is always the possibility of a breach of confidentiality. We will maintain patients' names, contact information (i.e., Identifiers), and all PHI (protected health information) in an encrypted computer database and all PHI identifiers will be removed in the database during data analysis. Every member of the Research Team is carefully trained and monitored about how to store, handle, and protect participant records.

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. Increased suicidality is possible during study participation.

Safeguards for Protecting Participants: Based on existing literature on tDCS, WET, and PTSD, we have developed exclusionary criteria and safety protocols to mitigate, regularly screen, and respond to possible risks that may occur during study participation.

tDCS: To safeguard against potential tDCS risks, we have developed exclusionary criteria related to the individual's medical, psychiatric, and substance use history and known contraindications to brain stimulation (see 7.1.2 Inclusion and Exclusion Criteria). Furthermore, prior to enrollment in the study, Melissa Martinez, MD (Co-I, medical attending) and Casey Straud, PsyD (PI) will review participants' assessment materials to confirm eligibility. In addition to eligibility determination, we will also implement safety procedures during study participation. Participants will be monitored for AEs at each treatment session and the one-month follow-up appointment. Reported AEs will be adjudicated at weekly study team meetings. In these meetings additional safety monitoring of a participant may be developed. Individuals will also complete the tDCS Reactions form at the end of each session to assess safety. Furthermore, the device includes programmable features (intensity and duration) to mitigate session variation and the tDCS equipment includes standardized presets for efficient and reliable electrode positioning. A study team member will also be in immediate proximity of the participant during tDCS should they require assistance or experience a serious AE. The device also has an abort button that can terminate the session and ramp down the current, as needed. Lastly, we will also monitor individuals for 15-30 minutes following tDCS prior to leaving the appointment. This portion of the appointment aligns with the WET protocol but allows for additional time to monitor the participant for AEs. In the event it is determined the individual requires emergency medical services, 911 will be alerted so that the individual can be taken to the nearest emergency department (e.g., University Hospital).

The risk for the mild itching sensation at the point of contact with the electrodes will be mitigated by excluding individuals with a history of skin condition, the use of saline solution, and limiting the intervention length to 30 min with ~1-week in-between sessions.

WET: Psychological distress experienced by participants is expected to be temporary and participants will be provided immediate coping tools and techniques to manage distressing emotions by the study therapist. Any indication that the participant is considering suicide, endorses active psychosis/mania, or other harm to self/others will be handled using evidence-based procedures and policies developed by the STRONG STAR Consortium. Participants who endorse mania/psychotic symptoms will prompt a clinical interview with a licensed clinical provider to assess current risk and risk of active mania/psychosis during study participation. Individuals with active mania/psychosis will be excluded from study participation. Trained clinicians and evaluators will assess history of suicide and current suicidal ideation using the Suicidal Ideation Thoughts and Behaviors Interview at the baseline assessment. Prior to each session individuals will also complete self-report questionnaires to monitor PTSD, depression, and suicidality symptoms. Participants identified as low to moderate risk for suicide based on the assessment results may be maintained on the 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).

For urgent issues that occur in between appointments, whether related to tDCS or WET, participants will be instructed to get help immediately by going to the nearest emergency room. All participants will be given a study device emergency department wallet card at the beginning of the study. Participants will be instructed to keep this card on their person throughout the study. The wallet card briefly describes the study intervention (tDCS vs. sham) and provides a study team contact number.

8.2 Potential Benefits. Potential benefits of participation in this study may include a reduction in, or amelioration of, PTSD symptoms over the course of therapy. Collectively, the possible risks (i.e., temporary increase in distress and severity) associated with participation are low and reasonable within this context given the level of participant monitoring and access to research and clinical staff. We believe that the possible benefits from participating in this study significantly outweigh the possible risks. The knowledge gained from this study will serve to inform the most effective early interventions for the prevention and treatment of PTSD in military veterans.

8.3 Alternatives. Other choices to participating in this study include: not participating in this study; receiving psychotherapy or medications in the community; or participation in other research studies involving experimental treatments.

9.0 ADVERSE EVENTS, UNANTICIPATED PROBLEMS, AND DEVIATIONS.

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

9.1 Reporting Unanticipated Problems Involving Risks to Subjects or Others, Serious Adverse Events and Deaths to the IRB Office. 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.

10.0 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 AE 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 medical treatment; 3) exacerbation of PTSD, anxiety, or depressive symptoms that the participant cannot tolerate; or 4) discontinuation would be in the participant's best interest. Participants deemed candidates for discontinuation will be discussed in conference calls with relevant study team members and will be brought to the attention of the PI and Co-I's for discussion and final decision. 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 AE, they will continue to be followed clinically by the therapist and/or member of the research staff until the AE is resolved or becomes stable. The reason the participants are discontinued from the study will be documented for future study planning.

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

The following table provides an overview of activities that the research team plans to accomplish. This funding mechanism is for two years. Funds will be transferred following IRB approval. Therefore, we have accounted for a 6 month "pre-award" period to submit for IRB approval, prepare study materials, and train staff in the table below, with the study time period initiating upon award transfer. We anticipate recruiting and treating 2-3 eligible participants per month to meet study goals.

	Pre Award	Start	Year 1				Year 2			
Study Activities (Months)	6 months		0-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24
IRB Approvals, Prepare Materials, Train Staff										
Recruit, Screen, and Treat 40 Participants			X	X	X	X	X	X		
Follow-up Assessments				X	X	X	X	X	X	
Data Cleaning and Analysis							X	X	X	X

12.0 STUDY CLOSURE PROCEDURES.

At the end of the study all data will be stripped of identifiers. De-identified (anonymized) data will be maintained indefinitely in the STRONG STAR Repository. Informed consent documents will be stored securely for a minimum of three years following completion of the research in accordance with 45 CFR 46 or in accordance with institutional requirements, whichever is longer. HIPAA authorizations will be stored for a minimum of six years in accordance with HIPAA regulations or in accordance with institutional requirements, whichever is longer. A Final Report will be submitted to the IRB to request inactivation of the study.

13. FUNDING.

This project is funded as part of a program award titled "Transcranial direct current stimulation for the treatment of post-traumatic stress disorder – from rodent models to clinical studies" through Center for Biomedical Neurosciences at UTHSCSA (Co-PIs: Casey Straud, PsyD, ABPP; Daniel Lodge, PhD; Flavia Carreno, PhD).

14.0 DESCRIPTION OF ASSESSMENTS.

The majority of the measures listed below are commonly used, have adequate to good psychometrics, and are part of the Consortium common data elements (CDE). As outlined in the National Research Action Plan, evidence-based CDEs and measures for STRONG STAR studies will ensure comparability of results across the consortium as well as other clinical trials and epidemiological studies of PTSD.

14.1 Clinical Interviews:

1. The Clinician Administered PTSD Scale for DSM-5 (CAPS-5). The CAPS-5 (Weathers, Blake, et al., 2013)is structured interview that assesses the DSM-5 criteria for PTSD. 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. 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. This measure will be administered at the baseline assessment and the one-month follow-up assessment.

2. Health Questionnaire. The Health Questionnaire includes items regarding physical and mental health history, diagnoses, utilization of services, and military medical board evaluation/VA disability. For this study, the Health Questionnaire will be modified to assess civilian and military participants. Participants are asked about current medications being used and provide information on how long they have been taking the medication. The Health Questionnaire also asks about caffeine use and frequency of use in the past month. Overall, this measure provides a brief, yet comprehensive overview of the patient's medical and psychiatric history as well as relevant information regarding caffeine use and medications. This measure will be administered at the baseline assessment and one-month follow-up.

3. Health Questionnaire tDCS Addendum. The Health Questionnaire tDCS Addendum is an adapted extension of the Health Questionnaire and includes items relevant to the assessment of tDCS health contraindications. Items will assess for history of seizures, significant intracranial pathology (e.g., severe traumatic brain injury), major neurological conditions (e.g., Dementia), metallic objects in the body, skin conditions where electrodes are applied that could be exacerbated (e.g., eczema), and adverse reaction to brain stimulation. This measure will be administered at the baseline assessment.

4. Self-Injurious Thoughts and Behaviors Interview (SITBI). The SITBI (Nock et al., 2007) is a structured interview assessing the presence, frequency, and characteristics of self-injurious and suicidal thoughts and behaviors. The SITBI 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 has shown high interrater reliability, test-retest reliability, and concurrent validity. This measure will be administered at the baseline assessment and the one-month follow-up assessment.

14.2 Self-Report Questionnaires:

5. PTSD CheckList-5 (PCL-5). The PCL-5 (Weathers, Litz, et al., 2013) 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 week (for all assessments during treatment) or the past two weeks (all other assessment time points) 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). This measure will be administered at the baseline assessment, prior to each therapy session, and the one-month follow-up assessment.

6. Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 (Kroenke et al., 2001) is a widely used and well-validated instrument for measuring the severity of depressive symptoms. 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 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) and correlates strongly with other measures of depression. This measure will be administered at the baseline assessment, prior to each therapy session, and the one-month follow-up assessment.

7. Generalized Anxiety Disorder Screener (GAD-7). The GAD-7 (Spitzer et al., 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) and has been shown to reliably discriminate between anxious and non-anxious diagnostic groups. This measure will be administered at the baseline assessment, prior to each therapy session, and the one-month follow-up assessment.

8. Posttraumatic Cognitions Inventory (PTCI). The PTCI (Foa et al., 1999) is a 36-item questionnaire that was developed to determine how an individual views the trauma and its sequelae in an attempt to understand both how PTSD develops and is maintained. Using an emotional processing theory, Foa and her colleagues have suggested that PTSD is a consequence of disruptions in the normal processes of recovery when an individual has excessively rigid concepts about self and world rendering the person vulnerable if a traumatic event occurs. Thus, the PTCI was developed as a measure of trauma-related thoughts and beliefs. It is comprised of three subscales (Negative Cognitions about the Self, Negative Cognitions about the World, and Self-Blame). The measure was tested in almost 600 adult volunteers recruited from two university PTSD treatment clinics as well as a university community. Approximately 65% (n=392) of individuals reported having experienced a trauma in which their own life or that of another person was perceived to be in danger and their response at the time included intense terror, horror, or helplessness (Criterion A event). The remaining 35% (n=162) denied such a traumatic experience. Of those who had experienced a trauma, 170 had PTSD symptoms of at least moderate severity while the remaining 185 reported a low symptom severity. The three subscales of the PTCI demonstrated internal consistency with alpha coefficients ranging from .86 to .97. Convergent validity was demonstrated comparing the PTCI to appropriate subscales of the World Assumptions Scale and Personal Beliefs and Reactions Scale. Significant correlations between the appropriate subscales ranged from .20 to .85. The PTCI was able to differentiate individuals with and without PTSD demonstrating discriminate validity (sensitivity = .78, specificity = .93). Test–retest reliability for each of the three subscales at a 1-week interval ranged from 0.75 to 0.89 and for a 3-week interval ranged from .80 to .86. This measure will be administered at the baseline assessment, prior to each therapy session, and the one-month follow-up assessment.

9. Depressive Symptoms Index-Suicidality Subscale (DSI-SS).The DSI-SS (Joiner & Metalsky, 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. A systematic review of measures of suicidal ideation and behaviors found that the DSI-SS had evidence of excellent internal consistency and concurrent validity. This measure will be administered at the baseline assessment, prior to each therapy session, and the one-month follow-up assessment.

10. Adverse Events Monitoring (AE). AEs will be assessed using the STRONG STAR AE monitoring procedures in order to evaluate safety of participants. Participants are asked, "Have you experienced any changes for the worse since your last visit?" All reported events are documented by the research team member. Participants also asked about the temporal nature (start/stop date), severity, impact on functioning, and whether the event is study-related or attributable to something else. AEs will be reviewed and adjudicated with the study team during weekly meetings to ensure reliable coding and participant safety. Melissa Martinez, MD (Co-I; Attending Physician and Casey Straud, PsyD (PI) will hold regular one-on-one meetings as needed to review medical-related AEs and monitoring of participants to mitigate health-related AEs during the study. AEs will be administered prior to each therapy session, and at the one-month follow-up assessment.

11. Transcranial Direct Current Stimulation (tDCS) Reactions Monitoring. tDCS reaction monitoring will be assessed using a STRONG STAR SOP for monitoring to evaluate safety of participants. Participants will be asked to complete the form self-report form at the end of the session. Participants who flag as at risk (elevated score on at least one item) on the form will be further assessed by a trained study therapist for safety. Individuals identified as at risk by study therapists will prompt a medical eyes on by the study nurse and/or Attending Physician to further determine the need for a higher level of medical

care.

12. Demographics Characteristics Form. The Demographics Form measures standard demographics (race, gender, age). This measure will be administered at the baseline assessment.

13. Life Events Checklist-5 (LEC-5). The LEC (Gray et al., 2004) includes a list of 24 potentially traumatic life events commonly associated with PTSD symptoms. The instrument was designed to facilitate the diagnosis of PTSD. 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). This measure will be administered at the baseline assessment.

14. Brief Inventory of Psychosocial Functioning (BIPF). The BIPF (Marx, 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." This measure will be administered at the baseline assessment, and the one-month follow-up assessment.

15. Quick Drinking Screen (QDS). The QDS (Sobell et al., 2003) will be used to assess hazardous or harmful patterns of alcohol consumption in the past two weeks. The QDS is a four-item screener that assesses average number of drinking days, average number of drinks on drinking days, number of heavy drinking days, and greatest number of drinks in a day over the past two weeks. The average total drinks consumed per week can also be calculated by multiplying items 1 (average number of drinking days per week) and 2 (average drinks per day). This measure will be administered at the baseline assessment and the one-month follow-up assessment.

16. Drug Abuse Screening Test-10 (DAST-10). The DAST-10 (Skinner, 1982) is a 10-item self-report instrument with strong validity and reliability that was adapted from the 28-item DAST. The DAST assesses maladaptive use of drugs over the past 12 months. Items are rated as "No" or "Yes". "Yes" responses are scored as "1" for all items except for item 3, which is reverse scored (No = "1"). Total scores are calculated by summing all items and can be interpreted as follows: 0 = no problems reported; 1-2 (low level); 3-5 (moderate level); 6-8 (substantial level); and 9-10 (severe level). The DAST manual recommends that total scores ≥ 3 warrant further evaluation for a potential substance use disorder. This measure will be administered at the baseline assessment.

17. Insomnia Severity Index (ISI). The ISI (Morin et al., 2011) 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 .74 and has shown convergent validity with other measures such as the Pittsburgh Sleep Quality Index (r = .67), the Dysfunctional Beliefs and Attitudes about Sleep (r = .55), and sleep diaries (r ranges from .32-.91). This measure will be administered at the baseline assessment and the one-month follow-up assessment.

18. Cognitive Emotions Regulation Questionnaire-short form (CERQ). The CERQ-short form (Garnefski & Kraaij, 2006) is an 18-item questionnaire that produces 9 subscales based on the original 36-item questionnaire. The CERQ self-report assesses cognitive coping strategies people tend to use, or what someone thinks, after having experienced threatening or stressful events. Item are rated on a 5-point Likert scale from 1 (almost never) to 5 (almost always) and produce nine subscale scores including: 1) Self-Blame, 2) Blaming Others, 3) Rumination, 4) Catastrophizing, 5) Positive Refocusing, 6) Planning, 7) Positive Reappraisal, 8) Putting into Perspective, and 9) Acceptance. The higher the subscale score, the more a specific cognitive strategy is used. The CERQ has good internal consistency and convergent validity across subscales. This measure will be administered at the baseline assessment and the one-month follow-up assessment.

19. History of Head Injuries (HHI). The HHI (Schwab et al., 2006) is a modified version of the Defense and Veterans Brain Injury Center (DVBIC) 3-Item Screening Tool. Item 1 assesses if an individual has a history of head injury, the count of head injuries, and what caused the head injury. Item 2 assess post concussive symptoms that were sustained at the time of the worst event. Item 3 assess if the individual is currently experiencing post concussive symptoms. The HHI is positive when the participant endorses a history of head injury (question 1) and altered consciousness (question 2, items A-E) from the worst head injury sustained. The form was modified for this study for civilian and military samples (i.e.,

deployment and non-deployment related head injuries were collapsed). The HHI has been identified as a gold standard for the diagnosis of TBI and has good concurrent validity. The HHI will be administered at baseline assessment.

20. Neurobehavioral Symptom Inventory (NSI). The NSI (Cicerone & Kalmar, 1995) is a 22-item measure of behavioral, emotional, and cognitive post concussion symptoms related to a traumatic brain injury. Participants rate the degree they are impacted by each symptom on a 5-point Likert scale from 0 (None-rarely if present) to 4 (Very severe-almost always present and I have been unable to perform at work, school, or home due to this problem. I probably cannot function without help). The NSI total score is a summed score of the items (0 – 88 range), with greater scores indicating greater impact. The NSI has demonstrated good psychometric properties (King et al., 2012). The NSI will be administered at baseline assessment and one-month follow-up assessment.

21. Numeric Rating Scale for Pain Intensity (NRSPI). The NRSPI consists of three separate items that assess current pain, pain at its worst, and pain at its best. Each Item responses range from 0-10 with higher scores suggestive of greater pain severity. There is no total score calculated for this measure. The NRSPI will be administered at baseline assessment and one-month follow-up assessment.

22. Patient Reported Outcome Measurement Information System - Pain Interference Short Form 8a (PROMIS). The PROMIS (Amtmann et al., 2010) measures the self-reported consequences of pain on relevant aspects of a person's life and may include the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. All items assess pain interference over the past seven days on a Likert scale from 0 (Not at all) to 5 (Very Much). The final score is represented by a T-score, a standardized score with a mean of 50 and a standard deviation (SD) of 10.The PROMIS has demonstrated good psychometric properties. Th PROMIS will be administered at baseline assessment and one-month follow-up assessment.

23. Credibility/ Expectancy Questionnaire (CEQ) for WET. The CEQ (Devilly & Borkovec, 2000) is a 6-item measure that was designed to assess treatment expectancy and rationale credibility for use in clinical outcomes studies. This measure has been utilized across a number of STRONG STAR treatment trials and can be easily adapted to assess the target intervention(s). For the current proposed study, the CEQ will be adapted to assess the credibility and expectancy for tDCS and WET. These constructs will be assessed separately using two measures specific to each construct. The 6-item CEQ assesses both whether the person cognitively understands how the therapy works (credibility) as well as whether the person affectively believes that the therapy will work for them personally (expectancy). The 6-item CEQ has been tested in 217 individuals including 68 male Vietnam veterans and 58 female spouses, 69 individuals diagnosed with general anxiety disorder who had received treatment, and 22 individuals who had received either Cognitive Based Therapy (CBT) or Eye Movement Desensitization and Reprocessing (EMDR) for the treatment of PTSD. The scale demonstrated high internal consistency (alpha coefficients ranged from 0.84 to 0.85). Test-retest reliability over a one-week period was found to be 0.82 for expectancy and 0.75 for credibility. The CEQ was able to differentiate between two treatment rationales in one study, one with and one without an encompassing theory while maintaining equivalence between three rationales in another study. Responses to four questions are scored using a 9-point Likert scale (1= not at all, 9= extremely). Responses to two of the questions are scored using an 11-point Likert Scale (0% to 100%). The combined responses are used to generate a score for credibility and another score for expectancy. This measure will be administered prior to the second session.

24. Credibility/ Expectancy Questionnaire (CEQ) for tDCS. The CEQ (Devilly & Borkovec, 2000) is a 6-item measure that was designed to assess treatment expectancy and rationale credibility for use in clinical outcomes studies. This measure has been utilized across a number of STRONG STAR treatment trials and can be easily adapted to assess the target intervention(s). For the current proposed study, the CEQ will be adapted to assess the credibility and expectancy for tDCS and WET. These constructs will be assessed separately using two measures specific to each construct. The 6-item CEQ assesses both whether the person cognitively understands how the therapy works (credibility) as well as whether the person affectively believes that the therapy will work for them personally (expectancy). The 6-item CEQ has been tested in 217 individuals including 68 male Vietnam veterans and 58 female spouses, 69 individuals diagnosed with general anxiety disorder who had received treatment, and 22 individuals who had received either Cognitive Based Therapy (CBT) or Eye Movement Desensitization and Reprocessing (EMDR) for the treatment of PTSD. The scale demonstrated high internal consistency (alpha coefficients ranged from 0.84 to 0.85). Test-retest reliability over a one-week period was found to be 0.82 for expectancy and 0.75 for credibility. The CEQ was able to differentiate between two treatment rationales in one study, one with and one without an encompassing theory while maintaining equivalence between three rationales in another study. Responses to four questions are scored using a 9-point Likert scale (1= not at all, 9= extremely).

Responses to two of the questions are scored using an 11-point Likert Scale (0% to 100%). The combined responses are used to generate a score for credibility and another score for expectancy. This measure will be administered prior to the second session.

14.3 Physiological/Biospecimen Measures:

25. Heart Rate. Heart rate will be assessed using a wearable Fitbit wrist watch device. Heart rate data can be beneficial for individuals who report subjectively being more aroused during the exposure or behaviorally appear to be more activated. Heart rate was selected because it is a robust physiological factor associated with PTSD and stress that can be measured affordably and without specialized expertise. Heart rate will be assessed continuously during the written exposure portion of sessions 1, 3, and 5.

26. Galvanic Skin Response. GSR will be assessed using a wearable Fitbit wrist watch device. GSR data can also be beneficial for individuals who report subjectively being more aroused during the exposure or behaviorally appear to be more activated. GSR was selected because it is a robust physiological factor associated with PTSD and stress that can be measured affordably and without specialized expertise. GSR will be tracked using a wearable device to assess the pre, post, and peak arousal levels during session. GSR will be assessed continuously during the written exposure portion of sessions 1, 3, and 5.

27. hCG Pregnancy Test. Pregnancy will be assessed at the baseline appointment using a human chorionic gonadotropin (hCG), CLIA-waived pregnancy test. hCG pregnancy tests are a reliable and valid measure of pregnancy that evaluates hCG levels in the blood or urine and can determine whether a person is pregnant, as well as whether their body is producing the right level of pregnancy hormones.

15.0 REFERENCES.

Ahmadizadeh, M. J., Rezaei, M., & Fitzgerald, P. B. (2019). Transcranial direct current stimulation (tDCS) for post-traumatic stress disorder (PTSD): A randomized, double-blinded, controlled trial. *Brain Research Bulletin*, *153*, 273–278. https://doi.org/10.1016/j.brainresbull.2019.09.011

Amtmann DA, Cook KF, Jensen MP, Chen W-H, Choi SW, Revicki D, Cella D, Rothrock N, Keefe F, Callahan L, Lai J-S (2010). Development of a PROMIS item bank to measure pain interference. *Pain 150*(1):173-82.

Asnaani, A., Reddy, M. K., & Shea, M. T. (2014). The impact of PTSD symptoms on physical and mental health functioning in returning veterans. *Journal of Anxiety Disorders*, *28*(3), 310–317. https://doi.org/10.1016/j.janxdis.2014.01.005

Benjet, C., Bromet, E., Karam, E. G., Kessler, R. C., McLaughlin, K. A., Ruscio, A. M., Shahly, V., Stein, D. J., Petukhova, M., Hill, E., Alonso, J., Atwoli, L., Bunting, B., Bruffaerts, R., Caldas-de-Almeida, J. M., de Girolamo, G., Florescu, S., Gureje, O., Huang, Y., … Koenen, K. C. (2016). The epidemiology of traumatic event exposure worldwide: Results from the World Mental Health Survey Consortium. *Psychological Medicine*, *46*(2), 327–343. https://doi.org/10.1017/S0033291715001981

Bikson, M., Grossman, P., Thomas, C., Zannou, A. L., Jiang, J., Adnan, T., Mourdoukoutas, A. P., Kronberg, G., Truong, D., Boggio, P., Brunoni, A. R., Charvet, L., Fregni, F., Fritsch, B., Gillick, B., Hamilton, R. H., Hampstead, B. M., Jankord, R., Kirton, A., … Woods, A. J. (2016). Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016. *Brain Stimulation*, *9*(5), 641–661. https://doi.org/10.1016/j.brs.2016.06.004

Cicerone, K., & Kalmar, K. (1995). Persistent postconcussion syndrome: The structure of subjective complaints after mTBI. *Journal of Head Trauma and Rehbilitation*, *10*, 1–17. http://dx.doi.org/10.1097/00001199-199510030-00002

Clark, C., Cole, J., Winter, C., Williams, K., & Grammer, G. (2015). A Review of Transcranial Magnetic Stimulation as a Treatment for Post-Traumatic Stress Disorder. *Current Psychiatry Reports*, *17*(10), 83. https://doi.org/10.1007/s11920-015-0621-x

DaSilva, A. F., Volz, M. S., Bikson, M., & Fregni, F. (2011). Electrode positioning and montage in transcranial direct current stimulation. *Journal of Visualized Experiments: JoVE*, *51*, 2744. https://doi.org/10.3791/2744

Davis, S. E., & Smith, G. A. (2019). Transcranial Direct Current Stimulation Use in Warfighting: Benefits, Risks, and Future Prospects. *Frontiers in Human Neuroscience*, *13*, 114. https://doi.org/10.3389/fnhum.2019.00114

Devilly, G. J., & Borkovec, T. D. (2000). Psychometric properties of the credibility/expectancy questionnaire. *Journal of Behavior Therapy and Experimental Psychiatry*, *31*(2), 73–86. https://doi.org/10.1016/s0005-7916(00)00012-4

Etkin, A., & Wager, T. D. (2007). Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *The American Journal of Psychiatry*, *164*(10), 1476–1488. https://doi.org/10.1176/appi.ajp.2007.07030504

Foa, E. B., Ehlers, A., Clark, D. M., Tolin, D. F., & Orsillo, S. M. (1999). The Posttraumatic Cognitions Inventory (PCTI). Psychological Assessments. *Psychological Assessments*, *11*, 303–314.

Foa, E. B., Rothbaum, B. O., Riggs, D. S., & Murdock, T. B. (1991). Treatment of posttraumatic stress disorder in rape victims: A comparison between cognitive-behavioral procedures and counseling. *Journal of Consulting and Clinical Psychology*, *59*(5), 715–723. https://doi.org/10.1037/0022-006X.59.5.715

Forbes, D., Bisson, J. I., Monson, C. M., & Berliner, L. (Eds.). (2020). *Effective Treatments for PTSD, Third Edition: Practice Guidelines from the International Society for Traumatic Stress Studies* (Third edition). The Guilford Press.

Fregni, F., Nitsche, M. A., Loo, C. K., Brunoni, A. R., Marangolo, P., Leite, J., Carvalho, S., Bolognini, N., Caumo, W., Paik, N. J., Simis, M., Ueda, K., Ekhitari, H., Luu, P., Tucker, D. M., Tyler, W. J., Brunelin, J., Datta, A., Juan, C. H., … Bikson, M. (2015). Regulatory Considerations for the Clinical and Research Use of Transcranial Direct Current Stimulation (tDCS): Review and recommendations from an expert panel. *Clinical Research and Regulatory Affairs*, *32*(1), 22–35. https://doi.org/10.3109/10601333.2015.980944

Fulton, J. J., Calhoun, P. S., Wagner, H. R., Schry, A. R., Hair, L. P., Feeling, N., Elbogen, E., & Beckham, J. C. (2015). The prevalence of posttraumatic stress disorder in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans: A meta-analysis. *Journal of Anxiety Disorders*, *31*, 98–107. https://doi.org/10.1016/j.janxdis.2015.02.003

Garnefski, N., & Kraaij, V. (2006). Cognitive emotion regulation questionnaire—Development of a short 18-item version (CERQ-short). *Personality and Individual Differences*, *41*(6), 1045–1053. https://doi.org/10.1016/j.paid.2006.04.010

Gray, M. J., Litz, B. T., Hsu, J. L., & Lombardo, T. W. (2004). Psychometric properties of the life events checklist. *Assessment*, *11*(4), 330–341. https://doi.org/10.1177/1073191104269954

Hertzog, M. A. (2008). Considerations in determining sample size for pilot studies. *Research in Nursing & Health*, *31*(2), 180–191. https://doi.org/10.1002/nur.20247

Joiner, T. J., & Metalsky, G. I. (1997). The Hopelessness Depression Symptom Questionnaire. *Cognitive Therapy and Research*, *21*(3), 359–384.

Kekic, M., Boysen, E., Campbell, I. C., & Schmidt, U. (2016). A systematic review of the clinical efficacy of transcranial direct current stimulation (tDCS) in psychiatric disorders. *Journal of Psychiatric Research*, *74*, 70–86. https://doi.org/10.1016/j.jpsychires.2015.12.018

King, P. R., Donnelly, K. T., Donnelly, J. P., Dunnam, M., Warner, G., Kittleson, C. J., Bradshaw, C. B., Alt, M., & Meier, S. T. (2012). Psychometric study of the Neurobehavioral Symptom Inventory. *Journal of Rehabilitation Research and Development*, *49*(6), 879–888. https://doi.org/10.1682/jrrd.2011.03.0051

Kraemer, H. C., Mintz, J., Noda, A., Tinklenberg, J., & Yesavage, J. A. (2006). Caution regarding the use of pilot studies to guide power calculations for study proposals. *Archives of General Psychiatry*, *63*(5), 484–489. https://doi.org/10.1001/archpsyc.63.5.484

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: Validity of a brief depression severity measure. *Journal of General Internal Medicine*, *16*(9), 606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x

Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: A practical primer for t-tests and ANOVAs. *Frontiers in Psychology*, *4*. https://doi.org/10.3389/fpsyg.2013.00863

Leon, A. C., Davis, L. L., & Kraemer, H. C. (2011). The role and interpretation of pilot studies in clinical research. *Journal of Psychiatric Research*, *45*(5), 626–629. https://doi.org/10.1016/j.jpsychires.2010.10.008

Lewis, C., Roberts, N. P., Andrew, M., Starling, E., & Bisson, J. I. (2020). Psychological therapies for post-traumatic stress disorder in adults: Systematic review and meta-analysis. *European Journal of Psychotraumatology*, *11*(1), 1729633. https://doi.org/10.1080/20008198.2020.1729633

Marin, M.-F., Camprodon, J. A., Dougherty, D. D., & Milad, M. R. (2014). Device-based brain stimulation to augment fear extinction: Implications for PTSD treatment and beyond. *Depression and Anxiety*, *31*(4), 269–278. https://doi.org/10.1002/da.22252

Marx, B. P. (2013). *Development and validation of a PTSD-related impairment scale.* www.dtic.mil/cgi-bin/GetTRDoc?AD=ADA585414

Morin, C. M., Belleville, G., Bélanger, L., & Ivers, H. (2011). The Insomnia Severity Index: Psychometric Indicators to Detect Insomnia Cases and Evaluate Treatment Response. *Sleep*, *34*(5), 601–608. https://doi.org/10.1093/sleep/34.5.601

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P. S., Fregni, F., & Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation*, *1*(3), 206–223. https://doi.org/10.1016/j.brs.2008.06.004

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*(3), 309–317. https://doi.org/10.1037/1040-3590.19.3.309

Pacella, M. L., Hruska, B., & Delahanty, D. L. (2013). The physical health consequences of PTSD and PTSD symptoms: A meta-analytic review. *Journal of Anxiety Disorders*, *27*(1), 33–46. https://doi.org/10.1016/j.janxdis.2012.08.004

Rahman, A., Lafon, B., Parra, L. C., & Bikson, M. (2017). Direct current stimulation boosts synaptic gain and cooperativity in vitro. *The Journal of Physiology*, *595*(11), 3535–3547. https://doi.org/10.1113/JP273005

Raij, T., Nummenmaa, A., Marin, M.-F., Porter, D., Furtak, S., Setsompop, K., & Milad, M. R. (2018). Prefrontal Cortex Stimulation Enhances Fear Extinction Memory in Humans. *Biological Psychiatry*, *84*(2), 129–137. https://doi.org/10.1016/j.biopsych.2017.10.022

Renshaw, K. D., Allen, E. S., Rhoades, G. K., Blais, R. K., Markman, H. J., & Stanley, S. M. (2011). Distress in spouses of service members with symptoms of combat-related PTSD: Secondary traumatic stress or general psychological distress? *Journal of Family Psychology*, *25*(4), 461–469. https://doi.org/10.1037/a0023994

Schwab, K., 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. *Neurology*, *66*(5), A235.

Skinner, H. A. (1982). The drug abuse screening test. *Addictive Behaviors*, *7*(4), 363–371. https://doi.org/10.1016/0306-4603(82)90005-3

Sloan, D. M., & Marx, B. P. (2019). *Written exposure therapy for PTSD: A brief treatment approach for mental health professionals*. American Psychological Association.

Sloan, D. M., Marx, B. P., Lee, D. J., & Resick, P. A. (2018). A Brief Exposure-Based Treatment vs Cognitive Processing Therapy for Posttraumatic Stress Disorder: A Randomized Noninferiority Clinical Trial. *JAMA Psychiatry*, *75*(3), 233. https://doi.org/10.1001/jamapsychiatry.2017.4249

Sloan, D. M., Marx, B. P., Resick, P. A., Young-McCaughan, S., Dondanville, K. A., Mintz, J., Litz, B. T., & Peterson, A. L. (2020). Study design comparing written exposure therapy to cognitive processing therapy for PTSD among military service members: A noninferiority trial. *Contemporary Clinical Trials Communications*, *17*, 100507. https://doi.org/10.1016/j.conctc.2019.100507

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*(6), 858–861. https://doi.org/10.15288/jsa.2003.64.858

Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: The GAD-7. *Archives of Internal Medicine*, *166*(10), 1092–1097. https://doi.org/10.1001/archinte.166.10.1092

Steenkamp, M. M., Litz, B. T., Hoge, C. W., & Marmar, C. R. (2015a). Psychotherapy for Military-Related PTSD: A Review of Randomized Clinical Trials. *JAMA*, *314*(5), 489. https://doi.org/10.1001/jama.2015.8370

Steenkamp, M. M., Litz, B. T., Hoge, C. W., & Marmar, C. R. (2015b). Psychotherapy for Military-Related PTSD: A Review of Randomized Clinical Trials. *JAMA*, *314*(5), 489. https://doi.org/10.1001/jama.2015.8370

Thair, H., Holloway, A. L., Newport, R., & Smith, A. D. (2017). Transcranial Direct Current Stimulation (tDCS): A Beginner's Guide for Design and Implementation. *Frontiers in Neuroscience*, *11*, 641. https://doi.org/10.3389/fnins.2017.00641

Thomas, J. L., Wilk, J. E., Riviere, L. A., McGurk, D., Castro, C. A., & Hoge, C. W. (2010). Prevalence of Mental Health Problems and Functional Impairment Among Active Component and National Guard Soldiers 3 and 12 Months Following Combat in Iraq. *Archives of General Psychiatry*, *67*(6), 614. https://doi.org/10.1001/archgenpsychiatry.2010.54

VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder: Clinician Summary. (2018). *Focus (American Psychiatric Publishing)*, *16*(4), 430–448. https://doi.org/10.1176/appi.focus.16408

van 't Wout, M., Mariano, T. Y., Garnaat, S. L., Reddy, M. K., Rasmussen, S. A., & Greenberg, B. D. (2016). Can Transcranial Direct Current Stimulation Augment Extinction of Conditioned Fear? *Brain Stimulation*, *9*(4), 529–536. https://doi.org/10.1016/j.brs.2016.03.004

van 't Wout-Frank, M., Shea, M. T., Larson, V. C., Greenberg, B. D., & Philip, N. S. (2019). Combined transcranial direct current stimulation with virtual reality exposure for posttraumatic stress disorder: Feasibility and pilot results. *Brain Stimulation*, *12*(1), 41–43. https://doi.org/10.1016/j.brs.2018.09.011

van 't Wout, M., Longo, S. M., Reddy, M. K., Philip, N. S., Bowker, M. T., & Greenberg, B. D. (2017). Transcranial direct current stimulation may modulate extinction memory in posttraumatic stress disorder. *Brain and Behavior*, *7*(5), e00681. https://doi.org/10.1002/brb3.681

Weathers, F., Blake, D., Schnurr, P., Kaloupek, D., Marx, B., & Keane, T. (2013). *Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) - PTSD: National Center for PTSD* [General Information]. https://www.ptsd.va.gov

Weathers, F., Litz, B., Keane, T., Palmieri, P., Marx, B., & Schnurr, P. (2013). *PTSD Checklist for DSM-5 (PCL-5) - PTSD: National Center for PTSD* [General Information]. https://www.ptsd.va.gov/