Management of Chronic Pain and PTSD in Gulf War Veterans With tDCS+Prolonged Exposure

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1. ABSTRACT (provide a one-paragraph summary of the current seed project)

Veterans with co-morbid chronic pain and PTSD utilize healthcare services at a higher rate than those with pain or PTSD alone. Unfortunately, there are no integrated treatments for Pain and PTSD. Moreover, non-pharmacological treatments for pain such as Cognitive Behavioral Therapy are useful in only about 50% of cases. Transcranial direct current stimulation (tDCS) may be an effective treatment for pain, and has been recently used to ameliorate PTSD symptoms. Prolonged Exposure Therapy (PE) is highly effective in treating PTSD symptoms. *Therefore, we propose to (a) integrate & (b) gather feasibility data for home-based tDCS + PE for Pain and PTSD with 15 Veterans.*

2. PRIMARY HYPOTHESES AND SPECIFIC AIMS (provide an NIH-style set of primary hypotheses about the project outcomes, and the specific aims that will be accomplished)

Chronic pain is one of the most prevalent health conditions among Americans, affecting about a third of the general population[1]. In Veterans, chronic pain is even more common, with a prevalence of about 50%[2,3,4,5]. For instance, the pain-related fibromyalgia diagnosis is part of Gulf War Syndrome and is highly comorbid with other common military service-related health problems such as Posttraumatic Stress Disorder (PTSD)[6]. Moreover, lack of effective, integrated, and available alternative treatments for chronic pain contributes to the opioid epidemic[7].Combat veterans are more likely to develop PTSD than civilians, with 20-30% of Vietnam-era Veterans, 15-25% of Operation Desert Storm Veterans, and 11-25% of Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn (OEF/OIF/OND) Veterans experiencing significant PTSD symptoms[8,9] The number of veterans with chronic pain and PTSD is expected to grow given the return of personnel from recent OEF/OIF/OND conflicts[9,10]. Veterans with co-morbid chronic pain and PTSD utilize healthcare services at a higher rate than those with pain or PTSD alone, leading to an increased burden on healthcare systems throughout the United States. Furthermore, opioid medications have been used more frequently to treat chronic pain among OEF and OIF Veterans with PTSD, and these Veterans are more likely to incur harmful consequences during the course of their care due to these medications[12].

The Overall Aim of the present proposal is to integrate, refine and investigate the feasibility (e.g., pilot testing, recruitment, attrition, assessment) of tDCS for treating chronic pain with a best practices evidence-based treatment for PTSD (i.e., Prolonged Exposure: PE) in 15 veterans, a group for which both pain and PTSD are particularly problematic.

SA1: *Integrate the home-based tDCS+PE Treatment*. The investigative team is comprised of Pain, PTSD, and salivary biomarker experts who will integrate tDCS into the 12 session PE treatment protocol.

H1: The 12 session PE protocol will yield itself well to tDCS component integration based on participant feedback.

SA2: *Test the feasibility of both the integrated intervention and key study design features, including translational research features such as biomarker assessment in a non-randomized trial with 15 Veterans assessed at baseline and post-treatment*. Feasibility of the home-based tDCS+PE intervention will be measured in terms of recruitment metrics, assessment burden, successful biomarker collection, specification of biomarker relationship to hypothesized mechanisms of change, treatment attrition, rates of missing data at each measurement time point, participant satisfaction, and ratings of treatment face validity. Post treatment key informant interviews will be conducted where suggestions for treatment enhancement and satisfaction will be systematically collected and analyzed.

H2 is given in terms of *Specific Pre-Defined Milestones for Success, including: 75% of Veterans experiencing chronic pain and PTSD who enroll will complete at least 8 sessions of the integrated treatment, and both completers and dropouts will offer actionable suggestions in exit interviews for improving the delivery of the intervention. **SA2)** Feasibility metrics will be acceptable for recruitment rate (two per month), treatment completion of 8 sessions (75%), assessment completion (90%), and good to excellent satisfaction (95%).*

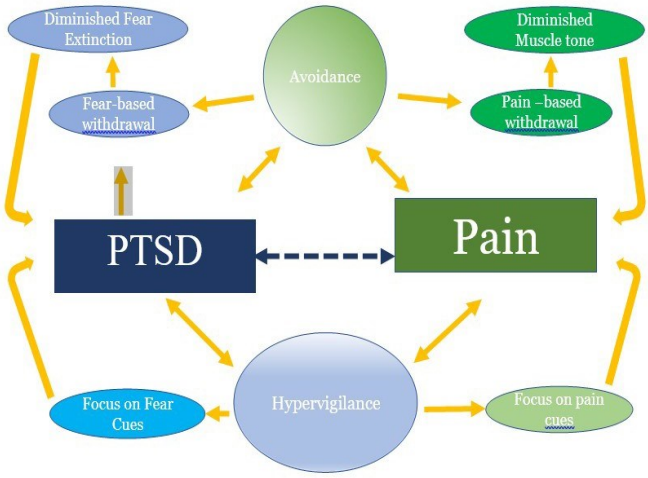
3. BACKGROUND AND RATIONALE (provide evidence for the importance of the scientific/clinical problem, and how this project will address the problem, including new knowledge to be gained)

Chronic Pain: Chronic pain is common in Veterans, with a prevalence of about 50%[2,3,4,5]. Moreover, pain is highly comorbid with other common military service-related health problems such as Posttraumatic Stress Disorder (PTSD)[6]. Pain is an exceedingly costly condition, with estimates from the Institute of Medicine at $560 to $635 annually for healthcare costs, disability days, and lost wages in the United States[10]. Moreover, lack of effective, integrated, and available alternative treatments for chronic pain is a contributor to the opioid epidemic[7].

Post-Traumatic Stress Disorder: PTSD is characterized by intrusion symptoms, persistent avoidance behaviors, negative alterations in cognition and/or mood, and alterations in arousal and reactivity[11]. Combat veterans are more likely to develop PTSD than civilians, with 20-30% of Vietnam-era Veterans, 15-25% of Operation Desert Shield and Desert Storm Veterans, and 11-25% of Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn (OEF/OIF/OND) Veterans experiencing significant PTSD symptoms[8,9].

3.1. Chronic Pain and PTSD: Potential for Mutual Symptom Exacerbation Avoidance of stimuli associated with a traumatic event, as well as hypervigilance (with concomitant increased pain perception) are diagnostic features of PTSD. Patients with chronic pain often exhibit avoidance behaviors secondary to perceived pain related to physical activity, leading to inactivity and weakened overall health status. Indeed, the presence of shared avoidance behaviors may predict poor outcomes for individuals experiencing co-morbid pain and PTSD[12,13]. Research focused on treatment approaches that address this shared avoidance may be fruitful, given the impact that co-morbid pain and PTSD have on veterans.

Figure 1



Hyperarousal and hypervigilance to bodily sensations are also found independently in chronic pain and in PTSD, although they likely have an additional synergistic effect on maintaining the negative impacts of both conditions when they are comorbid[12]. Additionally, other PTSD symptoms such as numbness and detachment from others are also frequently associated with chronic pain[14]. Figure 1 presents a thematic diagram illustrating the interaction between core characteristics of PTSD and comorbid pain targeted in the present proposal.

3.2. Transcranial direct current stimulation (tDCS). Noninvasive brain stimulation, such as transcranial direct current stimulation (tDCS), has received significant attention for the treatment of pain in chronic conditions owing to its neuromodulatory effects in the central nervous system[15].tDCS involves the application of low-amplitude direct electric current to the head in a noninvasive and painless manner, which modulates the resting membrane potentials of neurons, altering the excitability of the targeted cortical area. tDCS is categorized as a "non-significant risk" device by the U.S. Food and Drug Administration[16,17]. Hundreds of clinical trials have demonstrated tDCS to be safe and well tolerated within the established current intensities and durations[18]. For pain treatment, stimulation is typically delivered multiple times with the anode electrode placed over the primary motor cortex and with the cathode electrode placed over the supraorbital region. In particular, a panel of experts of the International Federation of Clinical Neurophysiology published evidence-based guidelines in which they recommended 20-minute tDCS using 2 mA electrical current intensity for possible efficacy among populations with chronic pain[19]. Our group and others have shown that this stimulation produces analgesic effects by activating afferents or efferents that connect structures involved in pain processing or by facilitating descending pain modulation and improves pain system function through direct effects on the motor, somatosensory, and frontal cortices implicated in pain sensitivity[20,21].

3.3. tDCS may potentiate treatment outcomes achieved from PE. Since tDCS is a noninvasive and safe approach to facilitate neuroplasticity[22], it may enhance the brain's ability to adaptively reorganize in response to other clinical interventions[23], including PE. Because the therapeutic effects of PE are at least partially due to adaptive changes in pain-related brain function, pairing tDCS with PE may augment the adaptive brain changes that occur with PE and further reduce pain and PTSD symptoms.

3.4. Saliva as a non-invasive Biomarker source for innovative Pain & PTSD related measures: Saliva contains numerous biomarkers including proteins, peptides, mRNA, DNA, and miRNA of both human and oral microbial origin[24,25,26,27]. Molecules such as nerve growth factor (NGF), substance P, dehydroepiandrosterone (DHEA), opiorphin[28] and calcitonin-gene related peptide (CGRP) are secreted in saliva in response to chronic stress and pain[29,30]. For instance, molecules such as cortisol, DHEA, Substance P, norepinephrine, salivary alpha amylase and estrogen have long been proposed to be useful in diagnosis of PTSD[31,32,33,34]. The following

are biomarkers that have been proposed to be indicative of development of PTSD symptoms, however not all of them were tested in the saliva (reviewed in Andrews, & Neises[35]): 1) Neuropeptide Y, released from sympathetic

neurons during chronic and sustained stress[36] 2) CD14, associated with TBI, stroke and microglial activity[37,38] 3) S100A8, marker of microglia and macrophages and elevated in TBI[39] 4) S100A10, shown to be reduced in level in PTSD when compared with controls[40,41] 5) TNFα, a potent inflammatory response initiator elevated in PTSD[42] (6) IL-1, associated with local and systemic inflammation, elevated in PTSD[43,44] 7) IL-6, a pleiotropic cytokine elevated in PTSD[45,46] and 8) GSα, a key intracellular signaling molecule associated with depression and suicide[47]. Recently salivary alpha amylase has been proposed to be a marker for pain in epilepsy[48] and cancer[49]; salivary cortisol and sTNFαRII have been to some degree associated with pain intensity and pain unpleasantness in healthy individuals[50]; salivary chromogranin A level increases after massage therapy suggesting it could be a marker for reduced pain perception[51]. Evidence shows the relevance of tDCS and salivary biomarkers. These studies show that tDCS stimulates salivary proteomic changes, especially related to inflammation and stress. For instance, IL-10, IL-6, TNF-alpha, CRP, Cortisol, and beta-endorphin have been shown to modify after tDCS treatment[52,53]. As the usefulness of these biomarkers has not yet been fully established in PTSD[54,34] further validation is critical.

4. INNOVATION

The means by which the current proposal addresses a widely prevalent problem (i.e., Pain comorbid with PTSD), and a national crisis (i.e., opioid addiction following pain treatment), is highly innovative, both in terms its treatment integration, and in terms of its use of select biomarkers to specify mechanisms of improvement.

5. METHODS (describe the primary plan for data collection, measurement tools, and timelines)

Design Overview and Project Timeline: The study team will first integrate home-based tDCS into two of the early weeks of the 12 week sessions of PE protocol. The reasoning to conduct tDCS in this way related to PE are three folded: first, controlling signaling of pain to engage into trauma treatment may reduce dropout from PE; second, research shows some cognition improvement with tDCS which may help patients to understand and more adequately participate in aspects PE treatment particularly as the complete understanding of the rationale of PE at the beginning of the treatment is very important to set the stage for treatment expectation and prevent dropout, and finally the hypothesized model of interaction of chronic pain and PTSD symptomatology, tDCS may help to reduce avoidance behavior modulated by pain and PTSD symptoms. This will be followed by a repeated measures single group design wherein each of the 15 Veteran participants serves as their own control, with major assessments of feasibility, clinical and biomarker indices at pre, mid and post-treatment (week 13), complemented by weekly assessments of key pain and PTSD symptoms. The study will also include with open ended key informant interviews following treatment with the 15 participants to derive suggestions for improving the integrated treatment

5.1. Study team: Dr. Hernandez Tejada, Principal Investigator, is an Associate Professor at the Department of Psychiatry, Trauma Resilience Center at UTHealth Houston and an affiliate Research Health Scientist at the Ralph H. Johnson VAMC in Charleston, SC. She is both a clinical psychologist and a health administrator and is currently site PI for a large Dept. of Defense PTSD treatment outcome study. Her work has centered on addressing dropout from evidence-based PTSD treatment and telemental health delivered psychotherapies for veterans. **Dr. Fries** is Assistant Professor at the Department of Psychiatry and Behavioral Sciences at UTHealth and an investigator at the Translational Psychiatry Program. Dr. Fries has a broad background in psychiatry, molecular biology, genetics, and biochemistry, with specific interest and training in epigenetics, bipolar disorder, and stress. Over the past few years he has been working on the search for the biological underpinnings of mood disorders, with an emphasis on epigenetics and biochemical mechanisms. He will be responsible for processing and analyzing the saliva samples. **Dr. Little**, is a professor in the Department of Psychiatry and the director of research for the Trauma and Resilience Center. Her current work involves Gulf War Veterans and focuses on the mechanisms that underlie risk for neurodegenerative disease secondary to brain trauma; development of diagnostic tests using high field magnetic resonance imaging for those who have been exposed to toxins during military service; and development of early interventions for PTSD. Dr. Little will facilitate with recruitment. **Dr. Ahn** is an Associate Professor in the Department of Research at the UTHealth Cizik School of Nursing and a board-certified nurse practitioner and nurse scientist with a strong background in electrical and computer engineering, and has produced more than 40 peer-reviewed publications (27 as first author). In particular, he has acquired professional training and earned certificates in neuromodulation (transcranial magnetic stimulation

and tDCS) and neuroimaging (multimodal brain imaging and fNIRS). He will be responsible for the tDCS component of this feasibility study.

5.2 Participants & Inclusion / Exclusion Criteria: Participants will be Veterans, age 18 years and older, presenting with PTSD and Pain. **Inclusion Criteria** are: 1) Presence of chronic non-cancer pain and pain interference, defined as scoring 1 standard deviation above PROMIS[55] normative data on both the 3-item PROMIS Pain Intensity 3a scale[55] and the 8-item PROMIS Pain 8a Interference scale[55] (see Measures below). Symptoms will be required to be of six-month duration or longer; 2) Diagnosis of PTSD assigned on the basis of the Clinician Administered PTSD Scale[56]. **Exclusion Criteria** are: 1) Having a household member who is already enrolled in the study; 2) Active psychosis or dementia at screening; 3) Suicidal ideation with clear intent; 4) Current substance dependence; 5) current opioid medication for pain 6) being pregnant.

5.3. Recruitment and Retention Procedures: will be addressed in the larger proposal derived from pilot.

5.4. Minority and Female Recruitment: At least 25% of the sample will be non-white and 10% female.

5.5. Description of the Informed Consent Process: Informed consent will be administered in private UTH TRC offices by approved individual trained in human subjects regulations and informed consent procedures. If any participants are illiterate, the consent will be read and explained in the presence of a witness. Teleconsent will also be used when the potential participant is unable to come to the office for the first visit of enrollment and to address unforeseeable circumstances, such as the current covid19 crisis. The potential participant will digitize (scan or photograph) a version of the consent they sign, or use a digital signature such as that found in Adobe to sign the consent document. This digitized document and signature will then be sent via email, or the hard copy will be sent via US postal service mail to the person consenting the potential participant.

5.6. Attrition and Retention efforts: Will be addressed in the larger proposal derived from this pilot.

5.7. Medication Stabilization. Patients will be asked to maintain medications at current dosages for at least 4 weeks prior to starting the trial.

5.8. Participant Payment: All participants will receive $30 for baseline and $30 for midpoint, $30 for the post-treatment clinical and biomarker assessments (insufficient time for follow-up), $15 for tDCS turn over and assessment, and $25 for the feasibility interview. Transportation/parking in the amount of $12 will be designated for the four in person visits.

5.9. Treatment: tDCS and PE Integration:

Overview of tDCS: tDCS is a non-invasive neuromodulation technique that has been used to improved cognitive functions. will be administered with a constant current intensity of 2 mA[57] for 20 min per session/ 10 sessions total daily for 2 weeks (Monday to Friday), the device is a Soterix 1x1 tDCS mini-CT Stimulator (Soterix Medical Inc., NY) with headgear and 5 _ 7 cm saline-soaked surface sponge electrodes. The sponge electrodes snap into the custom headgear, which is secured to the participant's head for simple and fail-safe electrode preparation. This single-position headgear with clearly labeled sponge markers eliminated room for user error and helped conserve the placement of the montage. Participants will administer a stimulation session via the Soterix 1x1 tDCS mini-CT Stimulator only after being provided a single-use code to unlock the device by the research staff once proper contact quality is achieved (only the on/off button will be adjustable by the study participants; they will not be able to adjust the device settings). After the participant enters the unlock code, the screen on the device will show a timer that counted down the minutes until the end of the session. After 20 min, the device will turn off automatically, and the study staff will instruct the participant to remove the headset and discard the sponges and to safely store all materials for the next session.

Overview of PE: Prolonged Exposure has been extensively researched, including by the present team (see Acierno et al.[58]), and is an effective treatment for PTSD[59] that includes the following components: a) psycho-education about the common reactions to traumatic events and presentation of the treatment rationale (sessions 1 and 2), b) repeated *in vivo* exposure to traumatic stimuli (in vivo exercises are assigned as homework during sessions 3 through 11), c) repeated, prolonged, imaginal exposure to traumatic memories (imaginal exposure is implemented during sessions 3 through 11; patients listen to session audiotapes for homework between sessions), and d) relapse prevention strategies and further treatment planning (session 12). The manual for PE is publicly available.

Integration of tDCS and PE: Participants will come in person to the clinic office to complete the baseline visit and the in-person training for the use of both home-based self-administered tDCS and the home-based telehealth device (iPad) for the PE sessions. They understand that they will start the sessions of tDCS once they start the in vivo and imaginal exposures assignments at home. They will self-administer (under televideo supervision) the

tDCS session before doing in vivo and/or imaginal exposures assignments. The participants will be remotely supervised by trained research staff at each stimulation to ensure the technique is correct and to monitor any adverse events. We will provide secure videoconferencing software (e.g., WebEx) and ensure the participants are comfortable using the telehealth software.

5.10 Dependent Measures / Feasibility, Biomarker, and Clinical (note description has been eliminated)

1. Demographics (pre-treatment only): age, race, ethnicity, sex, marital status, education, disability status, income, and employment information will be collected via a study specific demographic form.
2. Recruitment Metrics: defined as the rate of participant enrollment per week.
3. Biomarker Sample Collection: defined as the % of samples collected at major assessment points.
4. Feasibility of establishing biomarker relationship to hypothesized mechanisms of change: defined as ability to collect viable samples for analysis.
5. Treatment Attrition: defined as the % of participants dropping out prior to completing 12 sessions of the intervention protocol. We will also collect number of sessions completed.
6. Rate of Missing Data: defined as % of missing data (# missing items aggregated across all self-report measures divided by total number of possible items) at each measurement time point.
7. Treatment Satisfaction: as measured by the Charleston Psychiatric Outpatient Satisfaction Scale: CPOSS[60].
8. Treatment Credibility: defined as an overall scale rating from 0 to 10 with 0 being '*not credible, I did not think this treatment would help either my PTSD or Pain symptoms'* to 10 being "*completely credible, I was very sure this treatment would help both my PTSD and Pain symptoms*".
9. Treatment Acceptability: defined as an overall scale rating from 0 to 10 with 0 being '*not acceptable, this treatment should not be offered to veterans, those in pain, or those with PTSD*' to 'completely acceptable' "*this treatment is perfectly suited to veterans and others with Pain and PTSD symptoms*."
10. General Pain Information (Major Assessments): general information about chronic pain will be gathered to include location of pain site(s), duration of chronic pain at each site, current and prior treatment approaches for chronic pain, medical visits related to pain management, and past pain medications.
11. PROMIS Pain 3a Intensity Scale[55] (Weekly during Treatment + Major Assessments)
12. PROMIS PAIN 8a Interference Scale[55] (Weekly during Treatment + Major Assessments)
13. The Clinician-Administered PTSD Scale 5 (CAPS-5)[61] (Major Assessments)
14. PTSD Checklist-5 (PCL-5[61]) (Major Assessments)
15. PHQ-9[62] (Weekly during Treatment + Major Assessments)
16. World Health Organization Quality of Life – Short Form (WHOQOL-BREF)[63] (Major Assessments)

To permit comparison with prior pain research, but to limit participant burden, the following additional pain related scales will also be used only at major assessment points:

17. The West Haven-Yale Multidimensional Pain Inventory: (Major Assessments) (WHYMPI/MPI)[64]
18. The Tampa Scale of Kinesiophobia-Revised (TSK-R)[65] (Major Assessments)
19. Pain Catastrophizing Scale (PCS)[66] (Major Assessments)
20. Homework Diary (Weekly During Treatment): Daily records of tDCS and PE homework completion will be maintained so as to permit 'dose as delivered' effects of treatment.
21. Biomarker Assessments (Baseline, Mid-Point, Post-Treatment and Follow-ups)**:** Salivary levels of the biomarker panel (cortisol, substance P, DHEA, IL-1, and IL-6) using enzyme-linked immunosorbent assays (ELISA).

*Saliva Sample Collection (All major assessments)***:** Saliva samples will be collected through a passive drool method at the beginning and end of Baseline (first week), Mid-Point (week 6), and Post (week 12)-Treatment. Saliva will be naturally allowed to accumulate in the oral cavity and the participant will discharge it into the specimen tube (2 mL capacity) with lid.

Immediately after collection the collected saliva samples will be placed on ice and store at -80 degree C until analysis.

*Salivary Biomarker Measurement (All major assessments)***:** Owing to their possible involvement in pain and/or PTSD (see Background section), the following biomarker panel will be assessed in saliva: cortisol, substance P, DHEA, IL-1, and IL-6.

5.11. Post treatment Key informant interview procedures and Integration of Feedback

A standardized series of queries will be used to prompt participants to comment on various aspects of the intervention integration and how it might be approved. Additional information will be provided in the larger proposal derived from this pilot.

5.12. Treatment Providers / Interviewers / Consent Procedures: Project therapist will have a master's degree or higher in clinical psychology, counseling, or social work and be certified to deliver PE. All treatment sessions will be audio-taped and 15% of these will be randomly selected and rated for adherence. The PI or Research Assistant will conduct the consent procedures and initial eligibility (i.e., baseline) diagnostic assessments for the study. The Research Assistant will conduct all major assessments. All assessments will be audio-taped and study personnel will listen to a randomly selected 20% to ensure reliability of CAPS diagnosis over the course of the study. Pilot trials of this assessment battery indicate that major assessments will take between 75 and 90 minutes.

5.13. DATA ANALYSIS PLAN (provide a detailed description of how the data will be analyzed, focusing specifically on how the data analytic approach is suited to answer the study aims)

Analysis Sets & Treatment of Missing Data: Participants who terminate early will be asked to complete follow-up interviews and their data will be included in analyses following intent to treat standards.

Descriptive Analyses Putative prognostic variables that will be investigated through these descriptive analyses include: demographic factors, number/type of comorbid diagnoses, participation in non-study treatment for comorbid psychopathology, medications (by class), and initial (baseline) intensity/severity levels for the primary outcome variables: pain severity, pain interference, and intensity of PTSD (PCL), avoidance behaviors, and whether non-study treatments were received for psychopathology symptoms. To investigate potential limits on generalizability, we will compare demographic characteristics of those who decline to participate with those who participate.

Primary Feasibility Analyses *Feasibility Hypothesis SA1) 75% of Veterans experiencing Pain and PTSD who enroll in the Pilot will complete the integrated treatment (at least 8 sessions) and both completers and dropouts will offer actionable suggestions in focus groups for improving the delivery of the intervention.* We will report the % of veterans who complete the integrated tDCS+PE protocol. We will report the rate of treatment completion, including a description of number of sessions completed prior to dropping out at the patient level (with 12 sessions completed being 100% treatment complete/not dropout). In addition to overall measures of treatment completion (i.e., session attendance), we will also collect measures of treatment adherence, as measured by percent of returned, completed homework record forms for tCBS and exposure practices in terms of actual daily assignments completed. All these measures will also be reported in terms of Race and Sex. *Feasibility Hypothesis SA1) Feasibility metrics will be acceptable for recruitment rate (2 per month), treatment completion (75%), assessment completion (90%), and good to excellent satisfaction (95%).* A key feature of the proposed feasibility study is demonstration that recruitment of eligible participants is possible for a future large scale RCT. Thus, we will report all aspects of CONSORT data in addition to the number of referrals obtained each week. Finally, we will report the overall % of missing data at the item level, and the rate of assessment completion and partial completion at each time point to examine if assessment timing is optimal. SA1 also includes effective collection and use of stress biomarker samples. Finally, Descriptive data on rates / scores for satisfaction, credibility, and acceptability will be reported.

6. SUMMARY and SPECIFIC AIMS for ENSUING GRANT APPLICATION (Page 6)

SPECIFIC AIMS

Overview: Chronic pain is among the most pervasive and expensive health complaints in the United States[67,68]. Veterans, especially those who present with Post-Traumatic Stress Disorder (PTSD), are particularly likely to experience chronic pain[69,70]. Moreover, pain in the form of fibromyalgia diagnosis is actually a component of Gulf War Syndrome, and is highly comorbid with other common military service-related health problems such as Posttraumatic Stress Disorder (PTSD)[6]. While effective non-pharmacological treatments for each disorder exist independently[71,72], there are no integrated treatments for Pain and PTSD; this despite recognition of the primacy of pain complaints in combat Veteran populations[69]. Moreover, evidence-based non-pharmacological treatments for pain, per se, are effective in only about 50% of cases, with recent meta-analysis findings indicating no significant maintenance of effects at 6 or 12-month followup[73]. *Therefore, we propose to (a) refine & (b) gather feasibility data for an integrated mind-body intervention for Pain and PTSD: **tCBS+Prolonged Exposure**, with the prediction that integrating these treatments will enhance overall efficacy*.

Given its frequent co-occurrence with mental health conditions, pain is often conceptualized within a biopsychosocial model to explain the multiple dynamic and complex influences that impact its presentation and exacerbation[73]. Extending this model to PTSD supports the conceptualization of a mutual maintenance loop between pain and PTSD, and suggests the potential benefit, or perhaps, necessity of an integrated treatment for

both disorders, as common mechanisms may underlie symptom exacerbations for both Pain and PTSD[74]. Indeed, integrating innovative, non-pharmacological, non-invasive interventions such as tDCS with an evidence-based treatment for PTSD may produce short-term and long-term benefits in both PTSD and pain symptoms by addressing shared mechanisms.

Thus, the Overall Aim of the present proposal is to integrate, refine and investigate the feasibility (e.g., pilot testing, recruitment, randomization, attrition, assessment, etc.) of combining a non-pharmacological, non-invasive and short technique for treating pain (tDCS) and a best practices evidence-based treatment for PTSD (i.e., Prolonged Exposure: PE) in Veterans. Establishing feasibility will justify future work directed toward assessing the ability of the combined treatment to ameliorate the impact of shared hyperarousal and avoidance symptoms (e.g., pain mediated avoidance and anxiety/fear mediated avoidance; hyperarousal driven pain intensification). Moreover, standard psychological PROMIS measures of pain and PTSD will be complemented by stress-related salivary biomarkers before, during, and after treatment to test feasibility and relevance of these measures on pain ratings and PTSD symptoms. Whereas PE and the tDCS techniques already exist, the integration of these strategies into a treatment of acceptable duration, interaction and character must first be achieved and pilot tested as proposed here.

Toward this end, the Specific Aims of the present proposal are to:

SA1a: *Integrate and Pilot the tDCS+PE treatment*. The investigative team is comprised of Pain, PTSD, and salivary biomarker experts who will integrate tDCS and PE into a 12 session tDCS+PE treatment which will undergo subsequent pilot testing with 15 Veterans with significant ratings of pain and PTSD diagnosis. Post treatment key informant interviews will be conducted where suggestions for treatment enhancement and satisfaction will be systematically collected and integrated into the intervention.

SA1b: *Test the feasibility of both the intervention and key study design features*. The investigators will evaluate the feasibility of the integrated tDCS+PE intervention in treating Pain and PTSD measured in terms of recruitment metrics, randomization processes, assessment burden, salivary biomarker collection, specification of biomarker relationship to hypothesized mechanisms of change, treatment attrition, rates of missing data at each measurement time point, participant satisfaction, and ratings of treatment face validity..

SA2: *Observe a preliminary signal of treatment effects in terms of Pain and PTSD symptoms*. We will derive preliminary effect size approximations associated with intervention and comparison conditions in terms of primary symptom outcome measures.

Specific hypotheses include: SA1a) 75% of Veterans experiencing pain and PTSD who enroll in the Pilot phase will complete the integrated treatment and both completers and dropouts will offer actionable suggestions in focus groups for improving the delivery of the intervention. **SA1b)** Feasibility metrics will be acceptable for recruitment rate (4 per month), successful randomization (100%), treatment completion (75%), assessment completion (90%), and good to excellent satisfaction (95%). **SA2)** A preliminary signal based on baseline to post-treatment symptom changes for pain and PTSD measures will be acquired.

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