Remotely supervised tDCS for persistent post traumatic headache in Veterans (ReStore)

Funding Agency: RX-003194-01A1

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November 12, 2019

Abstract

Objectives: To evaluate the feasibility and efficacy of transcranial Direct Current Stimulation (tDCS) administered at home with real-time monitoring via VA Telehealth remote supervision for persistent post traumatic headache (PTH) associated with mTBI, and the impact of this treatment on functional recovery in Operation Enduring Freedom/Operation Iraqi Freedom veterans.

Methods: We will enroll 24 participants age 20-60 years old who meet the diagnostic criteria for persistent PTH associated with mild TBI. tDCS will be remotely administrated for a total of 20 sessions over a four-week period.

Primary endpoint: To evaluate the changes in numbers of moderate to severe headache days per month from baseline period to the end of treatment phase, and to the end of follow-up phase.

Secondary endpoints:

1. To evaluate the changes of total number of headache days per month, acute pain medication used based on number of doses of medication taken from baseline period to end of treatment phase, and to end of follow-up phase in the same cohort.
2. To evaluate the impact of headaches on the quality of life measures (pain and disability) based on change in Headache impact test-6 (HIT-6), Rivermead Post-Concussion Symptoms (PCS) questionnaire, depression severity as measured by PHQ-9, PTSD severity as measured by PCL-5, insomnia as measure by Insomnia Severity Index (ISI), and anxiety as measured by Beck Anxiety Inventory (BAI) from baseline period to end of treatment phase, and to end of follow-up phase in persistent PTH.
3. To evaluate the changes in modulatory capacity of patients' cardio-autonomic function as a measure of heart rate variability (HRV) from baseline period to end of treatment phase.

List of Abbreviations

Abbreviations used:

PTH - Post Traumatic Headache
mTBI – Mild Traumatic Brain Injury
OEF – Operation Enduring Freedom
OIF – Operation Iraqi Freedom
SN – Salience Network
CEN – Central Executive Network
ICHD – International classification of headache disorders
MOH – Medication Overuse Headache
HIT-6 – Headache Impact Test 6
PROMIS – Patient-Reported Outcomes Measurement Information System
PHQ-9 – Patient Health Questionnaire
BAI – Beck Anxiety Inventory
dlPFC – Dorsolateral Prefrontal Cortex
tDCS – Transcranial direct current stimulation
TMS – Transcranial magnetic stimulation
CGRP – calcitonin gene related peptide
CT – Clinical trial
PCL-5 – PTSD checklist for DSM-5
PCS – Rivermead Post-Concussion Symptoms
UI – User Interface
SMI – Soterix Medical Inc.

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1.0 Study Personnel (PI)

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2.0 Introduction

Background for Persistent PTH: Prevalence and incidence of mTBI and persistent post traumatic headache (PTH) are increasing among Veterans of Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) (McKenzie-Hartman 2017). Persistent PTH and associated physical, functional disability as well as decreased quality of life significantly impact OEF/OIF veterans. The recent opioid crisis raises concerns about medication overuse headaches in this population. Many OEF/OIF veterans are in the prime of their lives and are desperately in need of non-pharmacological treatment for this chronic debilitating neurological disorder, to lead a more productive life at work and home. Persistent PTH likely has multidimensionality: When headaches become persistent over years after mTBI, biopsychosocial and behavioral factors modulate the brain circuits beyond those involved in pain perception, resulting in dys-synchronization of intrinsic functional brain networks responsible for saliency modulation (salience network), goal directed behavior (executive network) and sense of self (default mode network). This process is likely similar to that of chronic migraine, as we have elucidated in a recent study (Androulakis et al. 2017, 2018).

Potential of remote tDCS for persistent PTH: The Veterans Health administration, US Department of Health and Human Services and Centers for Disease Control all support use of evidence based non-pharmacological treatment for chronic pain. tDCS (transcranial direct current stimulation) has gained attention as a noninvasive neuromodulatory approach for depression, chronic migraine, cognitive impairment involving attention, working memory and executive function, loss of inhibitory control, sleep disturbance and aphasia. (Kang, Kim, and Paik 2012; Demirtas-Tatlidede et al. 2012; Baker, Rorden, and Fridriksson 2010; Angelakis et al. 2014; Andrade et al. 2017). A systematic review and meta-analysis from 2016 suggest that tDCS could be a promising non-pharmacological alternative treatment for migraine pain. It may be particularly useful for individuals seeking to reduce the use of acute pain medications (Shirahige et al. 2016; Stagg and Nitsche 2011).

tDCS mechanism: The exact mechanisms underlying the effectiveness of tDCS in pain modulation are yet to be elucidated. Mounting evidence in pre-clinical and clinical studies suggests that tDCS can modify the neuronal excitability (Stagg and Nitsche 2011; Jackson M et al. 2016; Brunoni AR 2012) and is capable of improving connectivity of large-scale brain networks via improved synchronization (Peña-Gómez et al. 2012).

tDCS may modulate mu-opioid and GABA levels, interfere with excitatory and inhibitory balance by oscillating with intrinsic neural networks, as well as influence the cortical thalamic network in pain control (Jackson et al. 2016; Dasilva et al. 2012; DosSantos et al. 2014; DosSantos et al. 2012; Foerster et al. 2015). Clinical trials using remotely administered tDCS for Multiple Sclerosis (MS) and Parkinson's disease validated cumulative benefit of remote tDCS administration (Charvet et al. 2018; Dobbs et al. 2018). However, the effects of tDCS on persistent PTH have yet to be evaluated in remotely administered, at-home setting.

tDCS Stimulation Sites for persistent PTH: Analysis of one of our recent fMRI studies revealed that node to node functional connectivity of the bilateral dorsolateral prefrontal cortex (dlPFC) within the salience network (SN) and central executive network (CEN), important in top down cognitive control of pain (Androulakis et al. 2017, 2018), is abnormal in chronic migraine. Migraine and chronic migraine are the common phenotypes in persistent PTH. Earlier tDCS studies (outpatient clinic settings) in migraine used tDCS to: 1. Increase resting membrane potential in M1 via anodal stimulation, with the reference electrode placed over the contralateral supraorbital (SO) cortex, 2. Decrease resting membrane potential over Oz via cathodal stimulation with the reference electrode placed over Cz, and 3. Increase resting state membrane potential in the left dlPFC (dorsolateral prefrontal cortex) via anodal stimulation, with the reference electrode placed over SO (Andrade et al. 2017; Shirahige et al. 2016). **Among these different electrode configurations, left dlPFC was found to be more effective than left M1 for pain control**. We plan to place Cathodal electrode over Oz instead of contralateral OS because we want to avoid the possibility of inhibiting the contralateral PFC or interior frontal gyrus near the traditional cathodal site supraorbital (SO). **Mood irritability and disinhibition are frequent symptoms associated with mTBI and persistent PTH.** Inadvertently inhibiting brain regions near SO such as contralateral PFC or inferior frontal gyrus, which is important in behavior disinhibition, depression, and other neuropsychological symptoms prevalent in mTBI, may cause unwanted side effects. Given the lower threshold of neuronal excitability in occipital cortex of migraine patients (Aurora et al. 1998), we suspect that similar underpinnings may exist in persistent PTH. Interestingly, targeting cathodal stimulation site over Oz effectively reduced pain intensity in migraine patients (Antal et al. 2011). Furthermore, cathodal stimulation over Oz will effectively decrease cortical hyperexcitability in visual cortex without interfering the cortical descending inhibitory pathways on the contralateral side. **In this pilot study, we propose a novel electrode placement montage in which the stimulating (anodal) electrode is placed over the left dlPFC (F3) and a single reference (cathodal) electrode is placed over the lower occipital pole (Oz).** Our computational model demonstrates the current flow for this configuration(Figure 1).

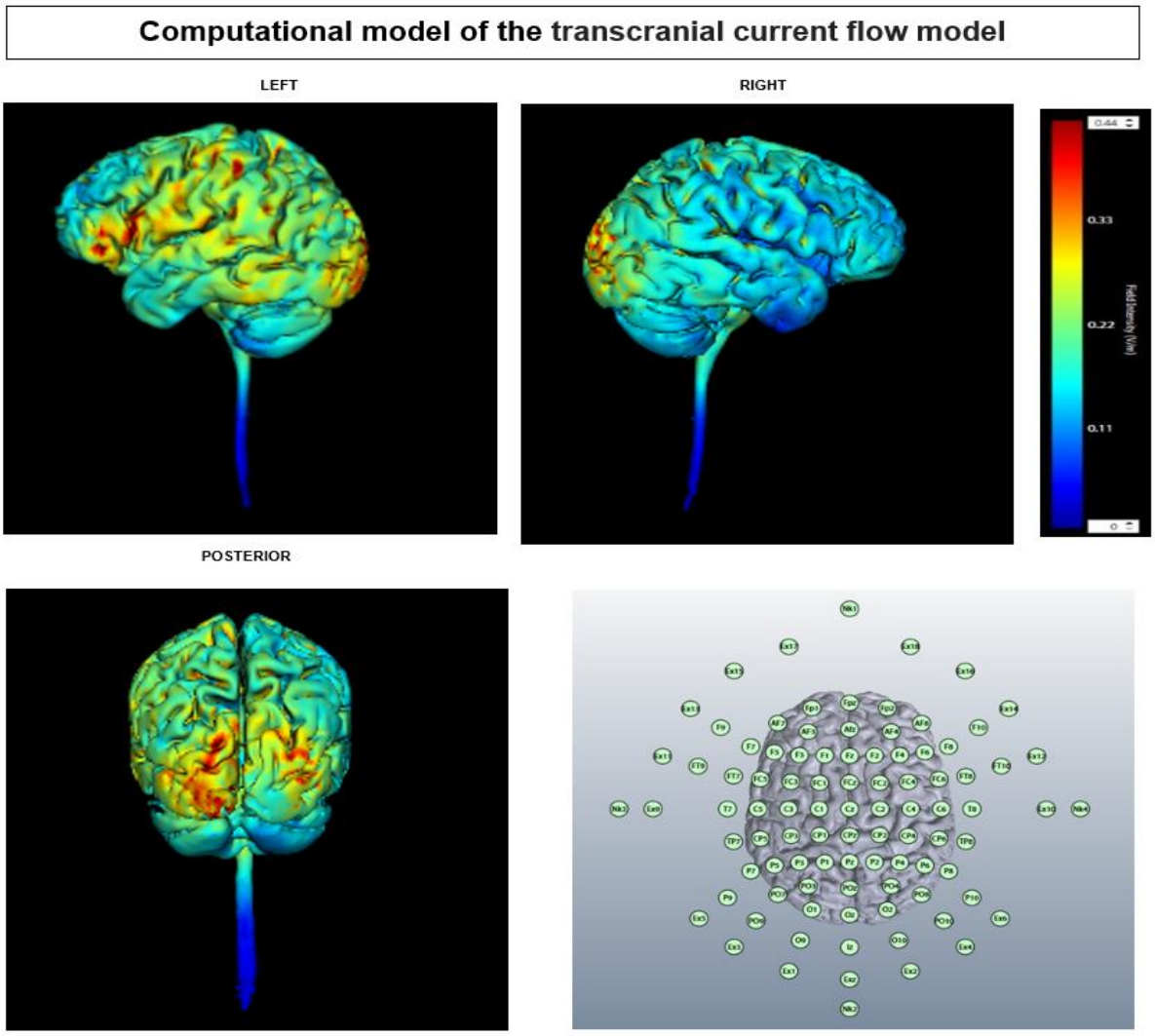


Figure 1: A computational model demonstrates the electrical field intensity using the tDCS mini Clinical Trial device: Anodal electrode placed over F3 (left dorsolateral prefrontal cortex), cathodal electrode placed over Oz.

Advantage of remote administration monitored by VA Telehealth: Remotely administrated tDCS with real-time video monitoring, delivered to veterans at home, offers unique advantages in terms of travel arrangement, healthcare utilization, increased treatment sessions, recruitment for future clinical trials with larger sample size, and preventing high dropout rates associated with tDCS administered in an outpatient setting. Furthermore, combining remote tDCS technology with mindfulness meditation via VA health system supported Mindfulness Coach program, and other cognitive/physical/occupational rehabilitation therapy may provide synergistic effects.

Multiple tDCS treatments are necessary for optimal and sustained benefit, especially when combined with cognitive training to enhance overall outcome (Kasschau et al.; Martin et al. 2014; Elmasry et al. 2015; Brunoni et al. 2014). **We propose a new clinical tDCS paradigm which will enable safe, longer, repetitive tDCS treatment combined with mindfulness meditation, while maintaining the treatment fidelity through video monitoring.** Based on the data generated from this pilot study, we plan to submit a larger scale, randomized clinical trial to investigate the efficacy of remotely administered tDCS with real-time monitoring for PTH in a phase II study. Ultimately, we hope that clinical application of this new delivery method of tDCS will facilitate outreach to rural communities, where Veterans have limited access to care related to persistent PTH.

3.0 Objectives

We propose to evaluate the feasibility and efficacy of transcranial Direct Current Stimulation (tDCS) (manufactured by Soterix Medical) administered at home with real-time monitoring via VA Telehealth for persistent post traumatic headache (PTH) associated with mTBI, and the impact of this treatment on persistent PTH associated functional recovery. This pilot study will also evaluate recruitment strategies and participants clinical characteristics. **We seek preliminary evidence for a merit review grant of a larger scale, randomized and sham controlled phase IIb clinical trial to evaluate efficacy of remotely administered tDCS for persistent PTH in veterans.**

Specific Aim 1:

To evaluate feasibility and improvement in numbers of moderate to severe headache days per month from baseline period to end of treatment phase, and to the end of follow-up phase.

Specific Aim2:

1. To evaluate improvement in total number of headache days per month and acute pain medication used based on number of doses of medication taken from baseline period to end of treatment phase, and to end of follow-up phase in the same cohort.
2. To evaluate the impact of headaches on the quality of life measures (pain and disability) based on change in Headache impact test-6 (HIT-6), Rivermead Post-Concussion Symptoms (PCS) questionnaire, depression as measured by PHQ-9, PTSD severity as measured by PCL-5, insomnia as measure by Insomnia Severity Index (ISI), and anxiety as measured by Beck Anxiety Inventory (BAI) from baseline period to end of treatment phase, and to end of follow-up phase in persistent PTH.

3. To evaluate the changes in modulatory capacity of patients' cardio-autonomic function as a measure of heart rate variability (HRV) from baseline period to end of treatment phase.

4.0 Resources and Personnel

The proposed research will be conducted at Dorn VA medical center, B106, Neurology Dept. . The PI will be responsible for overseeing all aspects of this project, including recruitment, screening, data collection, data analysis and preparation of manuscripts.

5.0 Study Procedures

5.1 Study Design

Participants will receive a total of 20 sessions with 20 minutes of tDCS stimulation administered during each weekday (see flow chart for details). The anode will be placed over the left dlPFC (F3) according to international 10-20 EEG system, and the cathode will be placed at Oz. Using this montage, computational modelling demonstrates the flow of current from left PFC region to the occipital pole, with no current flow over right PFC or inferior frontal cortex (Figure 1). Sham stimulation will be delivered using the conventional method of ramping the current up to 2.0 mA and the down over the first minute of the session and then repeated during the last minute of the session, no current are delivered in between. During the 20-minute treatment session, both treatment and sham groups will complete mindfulness meditation via VA health system approved program (Mindfulness Coach).

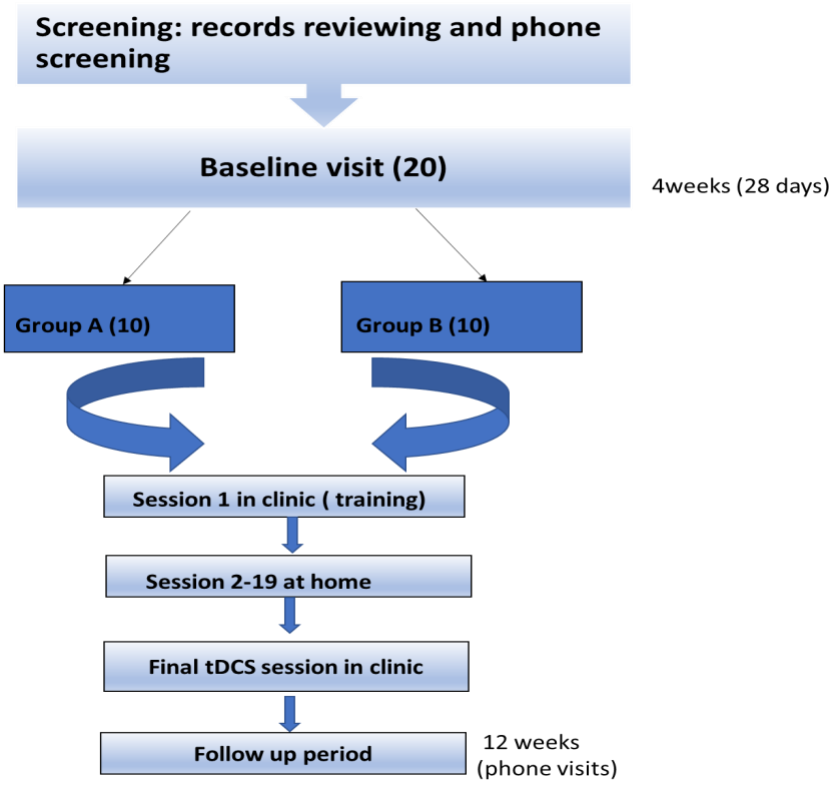
This will be a randomized, double-blind study of 20 tDCS treatment sessions. To ensure double-blinding of the study, the PI with designate a separate clinic nurse who is not part of the study team and is blind to group membership to be in charge of programming the tDCS device according to the device manual. The device will be programmed to subject's correct randomized treatment group. Patients will be randomized equally to stimulation group versus sham groups using randomization function with a statistical software (R). This person (nurse) will keep a secure randomization log and will not be involved in the screening, baseline, treatment sessions or follow-up visits. The blind may be broken if it becomes medically necessary to reveal which treatment a patient received. The investigator may contact any personnel within the randomizing group to request unmasking a subject's treatment.

All participants will undergo vital sign and BMI evaluation, a neurological examination and complete a medical questionnaire and to ascertain demographics including age, sex, race, marital status, educational level, and clinical characteristics to include: the headache features, medications, medical/surgical history, family history, HIT-6, Rivermead Post-Concussion Symptoms (PCS) questionnaire, depression severity as

measured by PHQ-9, ISI, PTSD severity as measured by PCL-5, insomnia as measured by Insomnia Severity Index (ISI), and anxiety as measured by Beck Anxiety Inventory (BAI). **Detailed descriptions for each questionnaire above are included in appendix**. A tolerability test using the tDCS device will be done at first clinic visit for each patient to confirm each subject can tolerate current stimulation. Patient that fail the tolerability task will be considered a screen-fail and will be discontinued from the study. Before the first and after the last tDCS session, participant's heart rate will be monitored via electrocardiogram (EKG or ECG) while completing a physical and cognitive stress test. This will enable us to determine changes in heart rate variability at the start of treatment to the end of treatment phases. **A more detailed description for the EKG tasks is included in Study Evaluations.** We will use the daily headache diary to record changes in headache symptoms throughout the study.

Due to the differences in how individuals describe pain, we will adopt the following definition for headache severity:

- Mild headache is defined as a nagging, annoying headache with little to no interference with daily activity.
- Moderate headache is defined as headache that is bothersome, interferes significantly with daily activity, and usually requires medication.
- Severe headache is defined as a disabling or intolerable pain that causes inability to perform routine daily activity (details are described in our patient questionnaires).



5.2 Recruitment Methods

We anticipate enrolling at least 4 participants quarterly, with a total enrollment period of 12-15 months. Veterans will be recruited from the Dorn VA neurology headache clinic or interdisciplinary outpatient pain clinic. Dr. Reyes, the Co-I of this project is the director of our OIPP pain clinic who sees about 80 PTH patients annually. Additional participants may be recruited from TBI clinic or TBI registry if necessary. A Real SSN Access Request has been submitted through DART for access to the TBI registry for pre-screening purposes. Potential subjects will be approached in clinics (neurology and rehab) by a member of the health care team or study personnel to assess interest in participating in the tDCS study. Recruitment flyers will be utilized in Neurology and rehab clinics. In addition, potential subjects identified through electronic medical records or clinic lists may be mailed a letter providing an overview of the tDCS study. An initial eligibility screen may be done via phone and will contain general information such as social demographics (i.e. age, sex, race), medical history and headache characteristics (appendix for PTH questionnaire). If the phone interview determines that the subject is potentially eligible, an appointment will be made for an in-person screening visit. Every effort will be made to include minority and women in this study.

Potential Benefits of the Proposed Research to Human Subjects & Others

Study participants may or may not benefit from their participation. All participants will receive tDCS (treatment vs sham) and mindfulness meditation. Self-efficacy may be greatly improved by providing encouragement to participants to take an active, autonomous role in their health. There is also monetary compensation for completing the tDCS sessions. There are potential benefits to other chronic post traumatic headache sufferers and to the scientific community, as we will develop a better understanding of the benefit and risk associated with at home tDCS administration. Given the paucity of risks, and the precautions and procedures to minimize those that do exist (as described in the previous section), this study is reasonable in relation to its anticipated benefits.

Importance of the knowledge to be gained

Results of the proposed research will make a significant contribution to the scientific knowledge regarding the feasibility and safety of remotely administrated tDCS for persistent PTH. The proposed clinical studies may lead towards identification of novel tDCS stimulation targets, utilization of telehealth for PTH, which help improve the management of persistent PTH.

Protection Against Risks

Notification of Screening Results: Participants will be notified that they have passed or failed the screening directly in person. This notification will occur as soon as information regarding eligibility becomes available. For example, if a screening failure occurs during an interview, the participant will be told that they do not meet study criteria and will be sent home without completing additional screening procedures. In the case of a screening failure, all documents containing a participant's personal health information will be destroyed.

Confidentiality: Every effort will be made to keep the information in the study confidential, as described in "Sources of Materials". In the case of screen failures, all documents containing the participant's health information will be destroyed. All data files and analyses will be performed on VA research computers using only code numbers to identify participants. Only summaries of group data will be reported in any publications or presentations, with no identification of individuals. Adverse Events: All adverse events will be reported to the IRB immediately by PI, Co-I or research assistant.

5.3 Informed Consent Procedures

Recruitment: All participants will be recruited from Dorn VA medical center neurology clinic. Additional participants may be recruited from TBI clinic and TBI registry if necessary. A HIPAA waiver will be applied for to permit use of the phone screen. If the phone pre-screening interview determines that the subject is potentially eligible, an appointment will be made for an in-person screening visit. Every effort will be made to include minority and women in this study.

Informed Consent: Written informed consent will be obtained by PI, Co-I, or research assistant/coordinators. The person obtaining informed consent will review the consent form in detail with the participants. The subjects will be encouraged to ask any questions they may have regarding the study and consent procedures. Once the subjects demonstrated an acceptable level of comprehension, consent will be obtained.

5.4 Inclusion/Exclusion Criteria

Inclusion criteria:

1. Verified history of mTBI using VA TBI identification clinical interview screening criteria (Vanderploeg et al. 2012),

2. Persistent PTH as defined by ICHD III diagnostic criteria (Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd Edition 2018).
3. Verification of headache frequency through prospectively collected baseline information during the 28-day screening/baseline phase.
4. Not currently taking a migraine or headache preventive medication OR has been taking a stable dose of a preventive for at least 60 days prior to screening and agrees to not start, stop, or change medication and/or dosage during the study period.
5. We will include medication overuse headache as defined by ICHD III diagnostic criteria.
6. Participant is either not of childbearing potential, or if they are of childbearing potential, they agree either to remain abstinent or use (or have their partner use) an acceptable method of birth control for the duration of the study.
7. Male or female, age between 20-60 who demonstrates compliance with the Daily Headache Diary during the 28-day baseline phase as defined by entry of headache data on a minimum of 22 to 28 days (80% diary compliance).

Exclusion criteria:

1. Unable to complete headache diary as required by protocol.
2. Any psychiatric condition with psychotic features, and/or any other psychiatric disorder not stable or well controlled, that would interfere in the ability to complete study activities
3. Received onabotulinumtoxinA, cognitive behavior therapy, physical therapy or any other form of non-pharmacological therapy for headaches during the 3 months before baseline and 4 months before the first treatment.
4. Has a planned military deployment within the 6 months post screening.
5. Active substance abuse within last 4 months.
6. History of seizure, stroke, multiple sclerosis or other unstable neurological condition or a significant abnormal neurological examination.
7. Unable to tolerate 2mA tDCS stimulation.
8. Have any other conditions that in the judgment of the Investigator would make the participants unsuitable for inclusion or interfere with participating or completing the study.
9. Does not have a valid email address and/or access to internet

5.5 Study Evaluations

tDCS Protocol: The first tDCS session combined with mindfulness meditation will be completed in the clinic after training on how to operate the device and a brief (60

second) tolerability test in clinic (some participants with sensitive scalps may be too uncomfortable to participate). Before the first tDCS session in the clinic we will utilize a standard 3-lead electrocardiogram (EKG) to measure participant's heart rate sequentially during a motor and cognitive task and at rest in order to assess heart rate variability (HRV) following tDCS treatment. This assessment, including set-up and transition between tasks, is expected to last approximately 30-35 minutes. The order of EKG measures will be as follows: 6-minute resting baseline, 6-minute physical stressor, 6-minute resting recovery, 6-minute cognitive stressor, and 6-minute resting recovery. During the resting assessments, participants will be seated comfortably at a 45-dregree angle while their heart rate is monitored. For the physical stress assessment, participants will squeeze a hand dynamometer (Baseline Pneumatic Squeeze Bulb Dynamometer, Baseline Products, Ventura CA) at approximately 30% of their maximum hand-grip contraction while seated in the same manner. During the cognitive stress assessment, participants will complete an executive function task (2-back task) while seated in the same manner. The 2-back task is a visual n-back test similar to the classic memory game. 2 back, n=2, has the person remember the item from two turns back. This task will be administered to the patient electronically via pc. Once the first in-clinic session is complete, participants will be discharged with a tDCS study kit (tDCS device, headset, sponges, saline solution, extra batteries). Participants will be given instructions on completing treatment sessions at home using the secure VA Telehealth platform and the VA mindfulness coach application. If participants don't have access to a tablet or computer at home they will be provided with a VA approved tablet with wireless connection during their participation in the study. Subsequent visits will be completed via the VA Telehealth platform with real-time supervision by a study coordinator or investigator. Participants will be supervised throughout the entire treatment session to ensure strict adherence to the device safety measures and study stop criteria (Charvet et al. 2017). Side effects and tolerability will be monitored at each visit by evaluating any adverse events such as pain, paresthesia, any other discomfort or any unexpected events. Headache severity ratings of mild, moderate or severe will be recorded before, during and after each tDCS session. Participants will return to the clinic to complete the last treatment session. During this last session, participant's heart rate will be monitored via EKG following the same procedures and tasks as stated above for the first in-clinic tDCS session. **The table below summarizes the procedures that will be done during each session throughout the study.**

Procedures	Baseline Visit	Treatment Phase			Post Treatment Follow-Up Phase
		Visit 2/First tDCS Session	Remote tDCS Sessions 2-19	Last tDCS Session 20	Daily Phone Calls (12 weeks)
Study Day	0	28 days		56 (+/-3)	57–140 (+/-3)
Informed Consent	X				
Neurological Exam	X	X		X	
Physical Exam	X	X		X	
Vital Signs	X	X		X	
EKG		X		X	
Verify Inclusion/Exclusion	X	X		X	
Medical History	X	X		X	
Diary Instruction	X				
Review Diary		X	X	X	X
Give/collect Telehealth tablet	X				*Participant will mail back tablet after last follow up
Train/Administer tDCS		X	X	X	
Collect Adverse Events		X	X	X	X
Demographics and Headache Surveys	X				
HIT-6		X		X	X (only weeks 4, 8, and 12)
PHQ-9 and BAI		X		X	X (only weeks 4, 8, and 12)
PLC-5 and PCS		X		X	X (only weeks 4, 8, and 12)
Insomnia survey		X		X	X (only weeks 4, 8, and 12)
Rivermead post-concussion symptoms (PCS)		X		X	X (only weeks 4, 8, and 12)

Mindfulness Coach: Both the stimulation group and sham group will receive mindfulness meditation using mindfulness Coach app during each tDCS session. Mindfulness Coach is designed for Veterans and Service Members and can be used alone or in combination with a trained health professional (App Version: 2.0).

Remote tDCS device and Safety: The Soterix Medical mini Clinical Trial (CT) device will to be used by patients at home in conjunction with constant real-time monitoring by clinical staff via VA Telehealth using well defined stop criteria (Charvet et al. 2018). Treatment parameters are pre-programed by accessing the 'administrator mode' to deliver 20 mins of 2mA stimulation during each session through sponge electrodes

(5cmx5cm). The administrator enters an access code and selects the tDCS dose: number of treatment sessions, intensity, and duration (10 participants will receive active stimulation applied to left dlPFC, 10 will receive sham treatment applied to left dlPFC, both groups will receive the same mindfulness meditation during the tDCS session). The administrator is then presented with a unique one-time activation code generated for each stimulation session. These codes will be stored at a secure location in our VA medical center. These parameters **cannot be altered** without the access code of the administrator, **any attempts to deliver un-authorized sessions (such as prolonged treatment session, atypical electrode impedance or any other administration of tDCS not specified by the study team) will results in device shutdown**. Electrodes impedance will be measured in real-time and displayed on the device screen and viewed by administrator during each session. Mini-CT tDCS can be remotely discontinued through its portal (ElectraRX program) if non-compliance is found during the treatment sessions. Patients will be given a package consisting customized headgear with electrodes (Anode on F3 and cathode on Oz), stimulation unit, sponges, and batteries. The unique electrodes (SNAP pad) allow loading onto headgear (SNAP strap) **at fixed locations preventing incorrect electrode placement and a picture will be taken at each session to confirm the stimulation sites.** The SNAP electrodes are pre-saturated with saline and carbon electrodes are pre-inserted **to prevent potential electrode preparation error**s (saline saturation level, direct contact of rubber electrode leading to skin burn, etc.). **The mini-CT device has extensive regulatory approvals worldwide (EU-CE, Canada- Health Canada, Australia, etc.) and is approved for investigational use in the USA.**

5.6 Data Analysis

Sample size and statistical analysis: A total of 24 veterans will be included in this pilot study. Descriptive statistics will establish baseline demographics, clinical characteristics, study completion rate (session discontinuation rate, and adverse event frequency. Comparison between treatment and sham control groups will be performed using two-tailed independent sample t-tests, and liner regression. Comparison of pretreatment and post-treatment scores in both groups will be calculated using paired-samples two-tailed t-tests. Statistical analysis will be performed using IBM SPSS Statistic 23. Reduction and extraction of HRV indexes from EKG assessments will be performed with Kubios HRV, version 2.0 (Biosignal Analysis and Medical Imaging Group, Kuopio, Finland).

5.7 Withdrawal of Subjects

As part of the consent process, subjects are advised that their participation to this study is voluntary and that they are free to withdraw their consent and discontinue participation in the study at any time throughout the study, without negative consequences to their relationship with their care at VAMC.

6.0 Reporting

Any unanticipated problems, serious adverse events, and protocol deviations will be reported to IRB within 24 hours of working day.

7.0 Privacy and Confidentiality

Every effort will be made to keep the information in the study confidential, as described in “Sources of Materials”. In the case of screen failures, all documents containing the participant’s health information will be destroyed. All data files and analyses will be performed on VA research computers with password protection using only code numbers to identify participants. Only summaries of deidentified group data will be reported in any publications or presentations following VA data management and access policy.

Adverse Events: All adverse events will be reported to the IRB immediately by PI, Co-I or research assistant.

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Amendment made to the original protocol

1. Due to COVID pandemic in 2020, all clinical trial activities in our facility was shut down for 6 months, subsequently our study was allowed to resume after changing the study protocol to minimize in-person clinic visit. As such, one of the secondary outcomes as removed from our Aims : evaluate the changes in modulatory capacity of patients' cardio-autonomic function as a measure of heart rate variability (HRV) from baseline period to end of treatment phase.
2. Additionally, we also changed last tDCS in-clinic visit to telehealth visit. Participants were provided prepaid labels to send the device / tablets back to research office after completion of all RS-tDCS sessions.
3. Lastly, we have changed post-tDCS follow up period to 4 weeks. In the original protocol, participants were followed up at 4 weeks, 8 weeks, and 12 weeks after tDCS/sham treatment. Due to significant burden of post traumatic headache on veterans with TBI, we have observed that many participants had difficulty to continue follow up after 4 weeks due to headache burden and desire to start new medication or non-pharmacological intervention for headache. Several participants even inquired about continuation of tDCS treatment. As such, we think withholding additional treatment 4 weeks after tDCS may negatively impact veterans' quality of life.

Patient Health Questionnaire (PHQ-9)				
During the last 2 weeks, how often have you been bothered by any of the following problems?				
	Not At All	Several Days	More Than Half The Days	Nearly Every Day
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3
Trouble falling or staying asleep, or sleeping too much	0	1	2	3
Feeling tired or having little energy	0	1	2	3
Poor appetite or overeating	0	1	2	3
Feeling bad about yourself - or that you are a failure or have let yourself or your family down	0	1	2	3
Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
Thoughts that you would be better off dead or of hurting yourself	0	1	2	3

For study coordinator: *0* +_____+_____+

= Total score:

If you checked off any problems, how difficult have these problems made it for you to do you work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

HIT-6 Questionnaire

This questionnaire asks about the effects your headaches are having on your life.
Please circle only one answer per question. The coordinator will score the questionnaire.

1. When you have headaches, how often is the pain severe?
   Never Rarely Sometimes Very Often Always
2. How often do headaches limit your ability to do usual activities including housework, work, school or social activities?
   Never Rarely Sometimes Very Often Always
3. When you have a headache, how often do you wish you could lie down?
   Never Rarely Sometimes Very Often Always
4. In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches? Never Rarely Sometimes Very Often Always
5. In the past 4 weeks, how often have you felt fed up or irritated because of yourheadaches?
   Never Rarely Sometimes Very Often Always
6. In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?
   Never Rarely Sometimes Very Often Always

_____	_____	_____	_____	_____	
Column 1 6 points ea.	Column 2 8 points ea.	Column 3 10 points ea.	Column 4 11 points ea.	Column 5 13 points ea.	TOTALSCORE

Scoring 48 or less = little or no impact
50-54 = some impact
56-58 = substantial impact
60+ = very severe impact

Beck Anxiety Inventory (BAI)

Below is a list of common symptoms of anxiety. Please carefully read each item on the list. During the last month (including today), how much have you been bothered by any of the following problems? Please circle the corresponding number.

	Not At All	Mildly, but it didn't bother me much	Moderately – it wasn't pleasant at times	Severely - it bothered me a lot
Numbness or tingling	0	1	2	3
Feeling hot	0	1	2	3
Wobbliness in legs	0	1	2	3
Unable to relax	0	1	2	3
Fear of worst happening	0	1	2	3
Dizzy or lightheaded	0	1	2	3
Heart pounding / racing	0	1	2	3
Unsteady	0	1	2	3
Terrified or afraid	0	1	2	3
Nervous	0	1	2	3
Feeling of choking	0	1	2	3
Hands trembling	0	1	2	3
Shaky / unsteady	0	1	2	3
Fear of losing control	0	1	2	3
Difficulty in breathing	0	1	2	3
Fear of dying	0	1	2	3
Scared	0	1	2	3
Indigestion	0	1	2	3
Faint / lightheaded	0	1	2	3
Face flushed	0	1	2	3
Hot / cold sweats	0	1	2	3

For study coordinator: _____*0*_____+_____+_____+_____= **Total score**:

PLC-5

Below is a list of problems that people sometimes have in response to a very stressful experience. Please read each problem carefully and then circle one of the numbers to the right to indicate how much you have been bothered by that problem in the past month.

In the past month, how much were you bothered by:	Not at all	A little bit	Moderately	Quite a bit	Extremely
1. Repeated, disturbing, and unwanted memories of the stressful experience?	0	1	2	3	4
2. Repeated, disturbing dreams of the stressful experience?	0	1	2	3	4
3. Suddenly feeling or acting as if the stressful experience were actually happening again (as if you were actually back there reliving it)?	0	1	2	3	4
4. Feeling very upset when something reminded you of the stressful experience?	0	1	2	3	4
5. Having strong physical reactions when something reminded you of the stressful experience (for example, heart pounding, trouble breathing, sweating)?	0	1	2	3	4
6. Avoiding memories, thoughts, or feelings related to the stressful experience?	0	1	2	3	4
7. Avoiding external reminders of the stressful experience(for example, people, places, conversations, activities, objects, or situations)?	0	1	2	3	4
8. Trouble remembering important parts of the stressful experience?	0	1	2	3	4
9. Having strong negative beliefs about yourself, other people, or the world (for example, having thoughts such as: I am bad, there is something seriously wrong with me, no one can be trusted, the world is completely dangerous)?	0	1	2	3	4
10. Blaming yourself or someone else for the stressful experience or what happened after it?	0	1	2	3	4
11. Having strong negative feelings such as fear, horror, anger, guilt, or shame?	0	1	2	3	4
12. Loss of interest in activities that you used to enjoy?	0	1	2	3	4
13. Feeling distant or cut off from other people?	0	1	2	3	4
14. Trouble experiencing positive feelings (for example, being unable to feel happiness or have loving feelings for people close to you)?	0	1	2	3	4
15. Irritable behavior, angry outbursts, or acting aggressively?	0	1	2	3	4
16. Taking too many risks or doing things that could cause you harm?	0	1	2	3	4
17. Being “super alert” or watchful or on guard?	0	1	2	3	4
18. Feeling jumpy or easily startled?	0	1	2	3	4
19. Having difficulty concentrating?	0	1	2	3	4
20. Trouble falling or staying asleep?	0	1	2	3	4

For study coordinator: 0 + _____ + _____ + _____ + _____ = **Total score**:

Insomnia Severity Index

The Insomnia Severity Index has seven questions. The seven answers are added up to get a total score. When you have your total score, look at the 'Guidelines for Scoring/Interpretation' below to see where your sleep difficulty fits.

For each question, please CIRCLE the number that best describes your answer.

Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?

Very Satisfied	Satisfied	Moderately Satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

6. How WORRIED/DISTRESSED are you about your current sleep problem?

Not at all Worried	A Little	Somewhat	Much	Very Much Worried
0	1	2	3	4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

For study coordinator:

Guidelines for Scoring/Interpretation

Add the scores for all seven items (questions 1 + 2 + 3 + 4 + 5 +6 + 7) =_____your total score

Total score categories:
0–7 = No clinically significant insomnia
8–14 = Subthreshold insomnia
15–21 = Clinical insomnia (moderate severity)
22–28 = Clinical insomnia (severe)

The Rivermead Post-Concussion Symptoms Questionnaire*

After a head injury or accident some people experience symptoms which can cause worry or nuisance. We would like to know if you now suffer from any of the symptoms given below. As many of these symptoms occur normally, we would like you to compare yourself now with before the accident. For each one, please circle the number closest to your answer.

0 = Not experienced at all
1 = No more of a problem
2 = A mild problem
3 = A moderate problem
4 = A severe problem

Compared with before the accident, do you now (i.e., over the last 24 hours) suffer from:

Headaches.....	0	1	2	3	4
Feelings of Dizziness	0	1	2	3	4
Nausea and/or Vomiting	0	1	2	3	4
Noise Sensitivity, easily upset by loud noise	0	1	2	3	4
Sleep Disturbance.....	0	1	2	3	4
Fatigue, tiring more easily	0	1	2	3	4
Being Irritable, easily angered	0	1	2	3	4
Feeling Depressed or Tearful	0	1	2	3	4
Feeling Frustrated or Impatient	0	1	2	3	4
Forgetfulness, poor memory	0	1	2	3	4
Poor Concentration	0	1	2	3	4
Taking Longer to Think	0	1	2	3	4
Blurred Vision	0	1	2	3	4
Light Sensitivity, Easily upset by bright light.....	0	1	2	3	4
Double Vision	0	1	2	3	4
Restlessness	0	1	2	3	4

Are you experiencing any other difficulties?

1._____	0	1	2	3	4
2._____	0	1	2	3	4

*King, N., Crawford, S., Wenden, F., Moss, N., and Wade, D. (1995) J. Neurology 242: 587-592