COVER PAGE – STUDY PROTOCOL

Title: Cranial electrotherapy stimulation: Piloting a road to PTSD prevention in first responders

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BUTLER HOSPITAL
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PROTOCOL

Project

Title of Project: Cranial electrotherapy stimulation: Piloting a road to PTSD prevention in first responders
Short Title of Project: CES in firefighters
Principal Investigator (PI): [redacted]
Other Investigator(s): [redacted]

Revision History:

Version Number	Version Date	Summary of Revisions
1.0	08/28/2023 09/18/2023	First version submitted First version approved
2.0	12/14/2023	1. Changed PI from [redacted]. 2. Added [redacted] as co-investigator to the study team. 3. Corrected error in ecological momentary assessment (EMA). 4. Added new advertisement material.
3.0	05/28/2024	1. Revised CNE Research Application to change Device Risk Level to "nonsignificant risk device" instead of "N/A". 2. Updated protocol to include XNAT – a password protected secure server – for transfer of MRI data from MRF to Butler. 3. Broadening of recruitment locations to include community locations (e.g. coffee shops).
4.0	8/15/24	1. Broadening of recruitment methods through social media marketing. 2. Update protocol to allow for texting for initial outreach to potential participants.

Description of Study

A. Specific Aims

Aim 1: Test the feasibility and acceptability of Cranial electrotherapy stimulation (CES) in firefighter first responders.
Prediction: CES is feasible quantified as more than 75% of sessions completed, and acceptable quantified as less than 20% attrition in the sample, such that at least 16 out of 20 firefighters complete, for example, at least 15 out of 20 sessions over the course of four weeks.

Aim 2: Test the effects of CES on subjective homeostatic functioning in firefighter first responders.
Prediction: CES will reduce subjective fatigue and frequency and intensity of negative emotions (e.g., distressed, nervous) while increasing the experience of positive emotions (e.g., calm, inspired) assessed naturalistically in near real-time through ecological momentary assessments (EMA).

Aim 3: Test the effect of CES on objective homeostatic functioning in firefighter first responders.
Prediction: Four weeks of CES will alter activation in the thalamus, as well as functional and structural connectivity in the default mode network. Additionally, we will pilot if CES improves measures of sleep quality and increase heart rate variability in a subset of participants.

B. Background

The prevention of posttraumatic stress disorder (PTSD) in first responders is of utmost importance. PTSD has a devastating impact on someone's life, and the intrusive symptoms and substantial psychiatric and medical comorbidity [1, 2] contribute to significant occupational and social dysfunction and reduced quality of life [3-5]. Due to the nature of their work, firefighter first responders repeatedly face traumatic experiences, and the prevalence of PTSD amongst firefighters may be as high as 37% [c.f. 6], with even higher rates for partial PTSD [7].

None of the current PTSD prevention strategies take a proactive approach where intervention starts irrespective of expected or prior trauma exposure. The current approaches to PTSD prevention can be divided into three main strategies, namely 1) adapting PTSD treatment protocols, such as brief cognitive-behavioral therapy, 2) the implementation of psychological debriefing (e.g., Critical Incident Stress Debriefing), or 3) the use of pharmacotherapy (e.g., benzodiazepines). Unfortunately, these approaches have either been met with limited success or are difficult to implement in first responders. Specifically, psychological debriefing has yielded relatively little efficacy in preventing PTSD, and the use of benzodiazepines has even been associated with a moderate increase in PTSD development [8]. Adapting cognitive-behavioral psychological interventions, where individuals process traumatic experiences by addressing (unhealthy) thoughts, feelings, and behaviors in response to trauma, have so far shown the most success in preventing PTSD [8]. However, the major downside of this approach is that these adaptive interventions, due to their intensity and characteristically trauma-focused content, are most suitable for individuals who already show (sub)clinical symptoms of PTSD, thus reflecting early intervention instead of proactive prevention. Additionally, during cognitive-behavioral therapy often a specific traumatic experience is targeted, with the assumption that this experience remains in the past. This is not the case in firefighters who, as first responders, continue to be repeatedly exposed to a wide range of traumatic events.

Cranial electrotherapy stimulation (CES) offers substantial promise as a proactive intervention for the prevention of PTSD. CES is a noninvasive neuromodulation technique that consists of pulsed, low-intensity current applied to the earlobes with demonstrated effectiveness for anxiety, insomnia, and depression as well as pain, compared to sham or waitlist control [9, 10]. Additionally, CES significantly reduced severity of PTSD symptoms [11] that persisted at one-month and three-months posttreatment [12] in military Veterans. CES has received FDA clearance as a class II device and has a highly favorable safety profile with minimal side-effects and exclusion criteria allowing broad application and, unlike many other noninvasive brain stimulation techniques, can be applied at home. Electrical field modeling shows that CES results in about 0.10 V/m peak induced cortical electric field with maximal currents in the medulla oblongata, and diffuse currents in the midbrain, pons, thalamus, insula, and hypothalamus [13]. Indeed, both 0.5- and 100-Hz CES resulted in significant deactivation in midline frontal and parietal regions, and both increased and decreased in connectivity within the default mode network [14], which is linked to introception and self-referential processes when the brain is 'at rest'. Furthermore, CES affects oscillatory brain activity associated with relaxed wakefulness [15], and may decrease serum cortisol level [16]. This is of high relevance to the pathogenesis of PTSD; our systems respond in a generalized, non-specific fashion to stressful and traumatic experiences, consisting of physiological and hormonal signals (e.g., the "fight-flight hormone" cortisol) to reestablish homeostasis. Over time, and with recurrent exposure, this homeostatic process becomes dysregulated in individuals who develop PTSD. Therefore, CES may promote (psycho)physiological homeostasis and lessens the negative consequences of (anticipatory) occupation-related stress and traumatic experiences by resetting the brain to pre-stress homeostasis. Indeed, in a recent study, 76 police and sheriff's officers as well as 10 firefighters reported very significant decreases in anxiety, insomnia, depression, and pain after CES [17].

Critical Gaps in Knowledge. Despite CES' potential for use in first responders, there are no studies that evaluate if a predefined four-week course of CES is feasible and acceptable in firefighters. Although one study examined CES in a sample of 86 first responders consisting mainly of law enforcement as well as 10 firefighters, participants were "permitted to use the device any time of day and for any indication" [c.f. 17] and the report does not mention of how often, at what time of day, and for how long participants used the device or whether

there were difficulties with its use, providing no information about feasibility or acceptability. This is important because it is advised to avoid the use of heavy machinery after CES. Therefore, the application of CES should be carefully integrated with the firefighter work schedules, starting with its use only on off-duty days. Additionally, there are no studies that test the effects of CES on subjective and objective indices of homeostatic functioning in active-duty firefighters to gain insight into possible mechanisms of CES-modulatory effects. In fact, despite a literature on effectiveness for anxiety, insomnia, and depression [but see 18 for a negative randomized controlled trial], the mechanism of CES effects on homeostatic functioning remains rather hypothetical with little direct evidence [19].

Here we propose to address these critical gaps in science by testing if a course of four weeks of CES in firefighters is 1) feasible and acceptable in this population; 2) impacts subjective variables associated with homeostasis, including fatigue, frequency and intensity of negative and positive emotions (i.e., distressed, nervous, calm, inspired); and 3) changes objective variables associated with homeostasis, including functional and structural neural connectivity, heart rate variability, and sleep quality in a subset of participants.

C. Experimental Method

C1. Brief Description of Subjects

Participants will be 20 active-duty firefighters in the State of Rhode Island, between 18-56 years old. Participants will be of any racial or ethnic group and of any gender.

C2. Study Design

This study will use a within-subject design, with all participants completing all experimental procedures with no difference to how CES will be applied. Recruitment of 20 participants incorporates an estimated 20% attrition to allow data collection on 16 participants.

During this study, eligible participants will be asked to come to Butler Hospital (2x) and may be asked to come to the MRI Research Facility at Brown University (2x) for a total of four study visits maximum. Participants will also be asked to self-administer CES during a four-week CES intervention period. During the first visit to Butler Hospital, participants will complete informed consent, screening measures, a semi-structured clinical interview, self-report clinical questionnaires, and practice 1) using the CES device for at-home use, 2) completing of EMA assessments to track subjective variables of homeostasis, and 3) using the Oura ring to track objective variables of homeostasis (only if available Oura rings fit correctly and comfortably on the participant's finger). During an optional second visit to the MRI Research Facility at Brown participants will undergo MRI scanning. Participants will then self-administer CES for four-week CES, after which they will return for a third optional visit to the MRI Research Facility at Brown for MRI scanning. All participants will complete the last visit to Butler Hospital for repeat clinical assessment as well as a debriefing about subjective experiences with CES, the Oura ring if the ring was used, and the EMA protocol. Study visits will vary in length between 1 to 3 hours.

Any ongoing treatment participants receive will be allowed to continue throughout the duration of the study. The to-be-used CES protocol follows device manufacturer guidelines.

C3. Specific Procedures or Treatments

Potential participants will be recruited from fire stations within the greater Providence metro area. Brochures and flyers using IRB approved language will be distributed at fire stations and various locations within the community (e.g., coffee shops, health centers, libraries, etc. where they allow posting on bulletin boards). Potential participants will be able to contact the research team to express interest. In addition, research team members will visit fire stations to increase awareness of the study and potentially interested individuals might provide their name and phone number for a research team member to contact them for further information –

contact information will be entered into a REDCap recruitment database (please see below for a description on the use of CNE REDCap in this study).

Pre-screening: Interested individuals will be provided with a brief description of the study and prescreened via brief telephone interviews. This prescreening interview will inquire about basic demographic information (e.g., name, age, sex), inclusion and exclusion criteria. Those meeting entry criteria will be invited to participate, and an appointment date/time will be arranged.

During Visit 1, at Butler Hospital, participants will provide information about demographics, complete safety screening for MRI and CES as well as complete self-report questionnaires, including the PTSD Checklist for DSM-5 (PCL-5) [20] to assess self-report severity of PTSD symptoms; the Inventory of Depressive Symptoms, Self-Report (IDS-SR) [21] to assess self-report depression severity; the State-Trait Anxiety Inventory (STAI) [22] to evaluate self-report symptoms of anxiety; the Pittsburgh Sleep Quality Index (PSQI) [23] to assess subjective quality of sleep prior to CES sue. The Quick Structured Clinical Interview for DSM-5 (QuickSCID) [24] will also be administered by a trained evaluator to assess for general psychiatric diagnoses and exclusion criteria. Finally, participants will be trained in how to complete EMA assessments, as well as use the Oura ring if applicable.

During Visit 2 (prior to four weeks CES) and Visit 3 (post four weeks CES), participants may undergo MRI scanning at the MRI Research Facility (MRF) at Brown University. These visits are optional and participants whose schedule does not allow to complete scanning during available hours at the MRF or who are not MRI eligible will not be excluded for these reasons (this will not hurt the goal of the study which is mainly to test feasibility and acceptability of CES use in this participant population). They will be required to sign a separate MRI consent form at the Brown Facility. When arriving at the facility the first 15 minutes will be used for familiarization with imaging procedures, safety assessment (if using nicotine products participants will be reminded that nicotine patches will need to be removed prior to MRI assessment), and participant placement in the scanner bore. In the scanner, foam wedges will be used to stabilize the participant's head to minimize motion artifact, and a cushion will be placed under the knees for additional comfort. This will be followed by a high-resolution multiecho MPRAGE structural scan. We will use multi-band echo-planar imaging to acquire Blood Oxygen Level Dependent (BOLD) fMRI resting state data. Two 12-minute scans will be obtained in phase encoding directions (A-P;P-A) to reduce field susceptibility bias while participants fixate on a crosshair rendered on a black screen. Additionally, we will collect diffusion tensor imagine data to further improve our understanding of possible neural network changes due to CES.

During Visit 4, at Butler Hospital, participants will complete repeat self-report measures from Visit 1 (e.g., PTSD, depression, anxiety, subjective quality of sleep) to assess potential effects of CES, a debriefing about subjective experiences with CES, the EMA protocol, and Oura ring if applicable.

Cranial electrotherapy stimulation (CES): We will use the Alpha-Stim AID device for CES following device instructions. The Alpha-Stim AID CES device has FDA clearance for treatment of anxiety and/or insomnia. During CES participants will have two ear clips attached to either ear to provide stimulation. Prior to placing the ear clip on each earlobe, participants will wipe their earlobes with an alcohol wipe and let them dry. These ear clips each include an electrode pad that will be moistened with the provided Alpha-Stim conducting solution until they are thoroughly saturated. Participants will then turn on the device, set the timer to one hour, and place each pre-wetted ear clip on their ears. CES includes a modified square, bipolar waveform of 0.5 Hz at 10-500 μA intensity, that will be individually adjusted to be below the threshold of mild tingling sensations and/or dizziness following device manufacture guidance and prior research [25]. Specifically, intensity will be individually set by asking participants to increase the current until a slight dizzy feeling is experienced, then decrease immediately until the dizziness stops. This individual adjustment of intensity will occur during the first study visit at Butler Hospital under the guidance of study staff. Study staff will go over the device manual, guide participants throughout the entire device set-up, and observe a practice CES session to

ensure participants understand all procedures as well as assess tolerability of the individually determined stimulation intensity prior to sending participants home with the Alpha-Stim AID CES device. The device manual, a quick set-up guide for ease of reference, as well as information on the determined intensity and a pen-and-paper tracking log will be provided to participants to be used during the four-weeks of at home administered CES. Throughout the four weeks of CES, participants will be asked to document the day, time, and duration of CES application using the provided tracking log. Participants will be instructed to only use the Alpha-Stim AID CES device on 'off-duty days' (i.e., days on which they are not working). This is done as an extra precaution to avoid potential negative effects of CES on work-related performance as using heavy machinery immediately following CES is not advised per device manufacturer. The research team will check in with the participant at least once per week (or more often if indicated based on incomplete EMA surveys or difficulties using the CES device), during the four weeks of CES, starting on the second day after starting CES. This check-in will allow obtaining feedback on user feasibility as well as allow assessment for the presence of side effects/adverse events. We will use a recently adapted Side Effects Questionnaire based on the one developed by Brunoni and colleagues [26]. Participants will also be provided with a contact phone number in case they experience side effects/adverse events prior to study staff check-ins or in case questions or other issues arise. Participants will be reminded that if they experience vertigo (a dizzy feeling, similar to the sensation of rocking on a boat) despite the predetermined intensity set during the in-person visit at Butler Hospital, they should decrease the intensity immediately until the dizziness stops.

Ecological Momentary Assessment (EMA): Participants will be asked to complete daily ecological momentary assessment (EMA) in which they self-report presence and intensity of emotional experiences based on the Positive and Negative Affect Schedule (PANAS, e.g., distressed, nervous, calm, inspired) and feelings of fatigue in their natural environment and in real time throughout the four weeks of at-home CES period. In addition to these daily surveys, the EMA survey will include additional questions related to the occurrence of potential traumatic/stressful events (e.g., accidents, fire, severe injuries) and how much participants are bothered by reminders, memories, avoidance, feeling easily startled, or negative beliefs of the stressful event, on a once weekly basis. EMA surveys will be sent to participants through an app to be installed on their smartphone using the company LifeData and which allows deidentified data to be stored online. Participants will be asked to complete an EMA survey every day to avoid overburdening participants while still being able to detect possible changes due to CES usage. EMA survey notifications can be silenced to avoid interference with work-related duties, and two reminder notifications will be sent to participants to allow completion of surveys at a later time when convenient before they expire. Study staff will reach out to participants by phone in case of non-compliance with EMA (e.g., two missed or incomplete surveys). These check-in calls serve to increase compliance and detect any possible issue(s) participants may have with completing EMA surveys.

Heart rate variability and sleep quality: A subset of up to 10 participants will be asked to wear an Oura ring while sleeping during off-duty days throughout the four week at-home CES period. A subset of participants will be randomly selected based on Oura ring fit and availability given that we will have a limited number and sizes of rings available. Participants will be asked to wear the Oura ring at night during off-duty days only to avoid accidentally wearing the Oura ring when responding to emergencies during night shifts as metal rings pose a safety hazard for firefighters. The Oura ring will capture measures related to sleep quality and heart rate variability over time. Participants will be explicitly informed that the Oura ring is not a medical device and is not intended to diagnose, treat, cure, monitor, or prevent medical conditions or illnesses (e.g., sleep apnea, heart conditions/arrhythmias). Although medical conditions can affect the data quality and result in missing data, so can other factors unrelated to medical conditions and we will not be able to infer why data is missing. Participants will be asked to install the Oura app on their smart phone to allow connection for data capture on sleep quality and heart rate variability. Data will be downloaded from the Oura Cloud web service or through the Oura API for further analyses.

C**4. Data Analysis**

The Project Leaders of this supplement, [redacted] will be responsible for and supervise data collection and data management. The main goals of this study involve assessing feasibility (i.e., > 75% of CES sessions completed) and acceptability (i.e., < 20% attrition in the sample) of a 4-week course of CES in active-duty firefighters (i.e., at least 16 out of 20 firefighters complete at least 15 out of 20 sessions over four weeks) and obtaining preliminary signal of effect to inform the design of a future, collaborative clinical trial to test efficacy of CES for the prevention of PTSD in first responders. Our primary outcome measures include the number of completed sessions to quantify feasibility and attrition in the sample assessing acceptability (Aim 1). In addition, we will collect data on subjective fatigue, negative and positive emotions using ecological momentary assessment (Aim 2) as well as heart rate variability and sleep quality (Aim 3). Finally, we will collect pre- and post-CES data on clinical symptoms (PTSD, depression, anxiety) and MRI-based resting state functional connectivity and structural connectivity (Aim 3). Given the preliminary nature, the proposed study is not designed to have adequate power to robustly test whether CES is effective for PTSD prevention, which would constitute the long-term goal of the proposed work. As such the proposed number of 20 individuals is solely meant to achieve the listed aims.

Data will be analyzed through t-tests and general linear models (e.g., (M)AN(C)OVA, repeated measures analyses, linear mixed models) using statistical software (e.g., SPSS, R, MPlus). To maintain anonymity in data files participants will only be listed with their unique identification code. Data backup of these files and hard copies of data capture forms will be kept in locked files to which only authorized study personnel will have access. Descriptive data will be provided for all participants (e.g., mean age, sex, education, etc.). Clinical rating scales will be scored as they are in clinical use. Interpretation of results will adjust for multiple testing to account for false discovery rates using step-down procedures where appropriate [87, 88]. EMA data will be aligned through a timestamp, permitting time parameterization of statistical models. Oura ring data is preprocessed by internal Oura algorithms (e.g., average HRV, Sleep score: REM, latency, deep sleep, restfulness) for comparison over time. All data will be examined for patterns and mechanisms of missingness prior to analyses to ensure missing data approaches are appropriate. For EMA data, we will use Blimp 2.1 to conduct multiple imputation for multilevel missing data prior to analyses. Multiple imputation using a Bayesian estimation approach or via full information maximum likelihood will be implemented as necessary for non-ecological data.

Electronic and/or digitized data (including PHI) will be stored on a password-protected server at Butler Hospital (e.g., COBRE), at the University of Rhode Island, and in CNE REDCap. This study will use Care New England's instance of REDCap for collection and storage of data. The study will not collect or store any actual data within REDCap until the project has been moved into REDCap's production environment. REDCap is a secure, web-based application developed by Vanderbilt University for building and managing surveys and databases. It is primarily designed to support online or offline data capture for research studies, quality improvement, and operations. REDCap provides easy data manipulation (with audit trails for reporting, monitoring and querying patient records), real-time data entry validation, and an automated export mechanism to common statistical packages. When data is downloaded, PHI will be removed and only an assigned code number will remain for analysis.

Care New England's instance of REDCap is hosted within the Care New England data center in Warwick, RI. This REDCap instance is role-based and is fully integrated with CNE's Active Directory structure. It enjoys 24/7/365 enterprise-level support and security inherit to CNE's HIPAA-compliant data center. Network transmissions (data entry, survey submission, and web browsing) to and from REDCap are protected via TLS 1.2 encryption. REDCap's data is stored on encrypted servers within CNE's data center. The REDCap Consortium is composed of thousands of active institutional partners in over one hundred countries who utilize and support REDCap. REDCap was developed specifically around HIPAA-Security guidelines, and more information about the consortium and system security can be found at http://www.projectredcap.org/.

De-identified MRI scans will be transferred from the computer in the scanner room at the MRF to XNAT - a password protected secure server – instituted by the MRF for secure transfer of MRI data.

D. Material Inducements

A total of up to $304 in compensation will be offered for the study-related procedures administered in this study. Participants will be compensated with $50 for completing Visit 1, $40 for each MRI session (Visit 2 and 3), and $50 for completing Visit 4. This totals $180 in compensation for study visits. In addition, participants will be compensated with $2 per CES session they complete (max 20 sessions; $40) and $2 for each EMA survey they complete, plus a weekly $5 bonus when they complete 6 out of 7 daily surveys each week (>85% EMA completion compliance, 4 weeks: 28 daily surveys ($2*28=$56) plus four weekly surveys ($2*4=$8) plus $5 weekly bonus ($5*4=$20) totaling to $84). Thus, participants can earn another $124 if they complete all EMA surveys and all CES sessions.

Compensation will be in the form of checks or gift cards, and will be provided after each Study Visit. If participants opt for compensation through checks, we will need to collect additional sensitive data (e.g., participant home address).

E. Training of Research Personnel

All research personnel will be trained to properly administer the study protocol by the PIs/ Project Leaders Drs. [redacted]. This training will specifically focus on administration of clinical measures, CES, and MRI, as well as the ability to train the research participants in the self-administration of CES. Drs. [redacted], as the Project Leaders will be responsible for documentation of training through sign off. All research staff will have completed research ethics training; including data management and procedures for maintaining data confidentiality and safety before being allowed to work on the project.

3) Human Subjects

A. Subject Population

Participants will be 20 active-duty firefighters within the State of Rhode Island. The Providence Fire Department is the largest fire department in the State of Rhode Island, employing about 400 firefighters, and is the second largest department in New England. No participant will be requested to change any medical care they might receive to participate in this study. Ongoing medical care will be recorded. In accordance with the NIH guidelines, efforts will be made to obtain a mix of study participants in terms gender, racial, and ethnic representation. Only participants who can give fully informed voluntary written consent will be accepted. Participants will be free to withdraw from the study at any time without penalty. Participants will be at minimum 18 years old and maximum 56 years old. The upper age limit of 56 is based on current practice in Rhode Island that firefighters are not older than 35 years of age when they become a firefighter and that firefighters can retire after 20 years of duty. As such most firefighters will have retired from active duty at age 55. We included a one-year margin to avoid excluding participants who turn 56 during the study.

Study inclusion criteria include:

(1) active-duty firefighter in the State of Rhode Island;
(2) age between 18-56 years;
(3) be in good medical health or, if having chronic medical conditions, these conditions need to be stable;
(4) ability to speak, read, write, and understand English sufficiently well to complete study procedures and provide informed consent.

Study exclusion criteria include:

(1) CES-related contraindications, e.g., implanted metallic device or substances including pacemakers, implanted or wearable defibrillators, pregnancy or planning to become pregnant during the study duration;

(2) neurological conditions such as brain neoplasm, cerebrovascular events, epilepsy or history of seizures, dementia, and neurodegenerative disorders, or had previously received brain surgery;
(3) report presence of suicidal ideation on QuickSCID-5 or has attempted suicide one or more times within the past twelve months;
(4) exhibiting a psychiatric condition that would require inpatient or partial psychiatric hospitalization;
(5) current moderate or severe alcohol or other substance abuse (excluding nicotine and marijuana);
(6) major or unstable medical illness requiring further investigation or treatment;
(7) do not own a smartphone or not able or willing to install EMA and/or Oura ring app on personal smartphone;
(8) inability to operate the CES device after training and/or intolerability to CES during in office session on Visit Day 1.

If asked to complete MRI scanning, participants will be screened for MRI eligibility criteria, e.g., no cochlear implant, metallic tattoos, undefined metal in the body, claustrophobia, pregnancy. However, not being able to complete MRI is not an exclusion for participation.

B. Recruitment and Consent Procedures

Potential participants will be recruited from fire stations within the greater Providence metro area. Brochures and flyers using IRB approved language will be distributed at fire stations, and through social media advertisements. Potential participants will be able to contact the research team to express interest. In addition, research team members will visit recruitment sites (e.g., fire stations) to increase awareness of the study and potentially interested individuals might provide their name and phone number for a research team member to contact them for further information.

Individuals who inquire about participation will be contacted by study staff by phone call, or text from the designated study cell phone for initial contact. Individuals will be provided with a brief verbal description of the study, and invited to participate if they appear eligible based on pre-screening. At the beginning of Visit 1, participants will meet with study staff in a private room and will be provided with a written explanation of study procedures, risks, and benefits and research staff will carefully explain all aspects of the study, including potential risks and benefits, and the expected duration and time commitment of their participation. Participants will be given the opportunity to ask any questions they may have, take as long as they need to decide if they want to participate (e.g., they can take the consent form home to think it over), and if they remain interested, written informed consent will be obtained by a member of the study team who has received training in the protection of human research participants. Participants will receive a copy of the informed consent document including contact information, should any questions or concerns arise at a later time. After informed consent is obtained, participants will be further evaluated to confirm eligibility.

C. Potential Risks

Potential risks to all subjects include:

(1) Breach of confidentiality or loss of privacy. In the course of this study we will collect sensitive information which, if released, may cause shame, embarrassment, or distress. Additionally, due to the nature of at-home CES, EMA, and Oura ring (if applicable), colleagues, family members, and/or friends might find out about study participation which might be uncomfortable.
(2) Distress due to assessment procedures: Asking participants about their thoughts, feelings, behaviors, and potential psychiatric symptoms during the clinical interviews, completion of rating scales, and during the EMA surveys might increase distress or result in discomfort.
(3) Perception of coercion to participate in the study: Participants may feel coerced to participate.
(4) MRI: The bore of an MRI scanner is narrow, which can cause a claustrophobic reaction in some participants. For the real scanner there is the additional small risk that participants will experience heating

during the scan from exposure to radio frequency (RF) coils. Furthermore, there are risks associated with MRI scanning associated with metal implants near the magnet, including metallic tattoos. Finally, there is the risk of discovery of unknown potential health problems. During the MRI procedures, it is possible that signs of a previously unknown health problem may be discovered (e.g., images that contain possible lesions, tumors, cerebrovascular problems) that may cause distress.

(5) CES: CES is considered a low-risk technique that is well tolerated and carries minimal to no side effects. CES devices are FDA cleared as Class II devices. The to-be-used CES device (AlphaStim AID) can be purchased online by individuals from the company website (for US customers a 'doctor's note' is required but this can be arranged online on the company website at time of purchase – in the proposed study, release of the device to participants will be provided by physicians in Butler's Neuromodulation Research Facility, following company purchasing practices). Side effects from CES are mild and self-limiting (<1%). The most common side effects include vertigo, nausea, and headache [16, 25], although skin irritation at electrode sites, ear pain, tingling, pulsing or tingling sensations on ears, and tender ears have also been reported. In a large trial in 115 participants with anxiety disorder and comorbid depression reported no adverse events using the Alpha-Stim CES device we propose to use in the current study and with identical settings [27]. CES is thought to be safe without risk of seizure induction in the absence of neurologic risk factors. CES is contraindicated with implanted pacemakers or implanted or wearable defibrillators and pregnancy as safety of stimulation has not been established during pregnancy. It is advised not to use dangerous machinery or vehicles during treatment, and in some cases following treatment.

(6) EMA: EMA surveys might be frustrating because they ask the same things multiple times. EMA survey notifications delivered during working hours can cause distraction.

(7) Oura ring: The Oura ring is made from metal and as with any ring, skin irritations or difficulty removing the ring can occur. The Oura ring contains a battery, and when working with batteries, or devices and/or with machinery that contain batteries while wearing the Oura ring, there is a risk of a short circuit when both the cathode and the anode of another battery touch the ring. This can result in a potentially dangerous shock. The Oura is a radio transmitter and receiver. It's designed not to exceed the emission limits for exposure to radio frequency (RF) energy set by the Federal Communications Commission. Ring EMF frequency has an SAR (Specific Absorption Rate) level of 0.0003 W/kg, compared to an SAR level at or below 1.6 W/k for all cell phones sold in the United States.

(8) Inconvenience and burden of required time/travel: Travel to Butler Hospital and/or the Brown MRI Research Facility may represent an inconvenience.

(9) Other: There may be other risks not currently known. For example, participation in this study includes possible worsening of clinical symptoms.

D. Protection of the Subject

D1. Measures to Minimize Potential Risks

(1) Breach of Confidentiality: Breach of confidentiality is highly unlikely because all data are identified only by numeric code and are stored in locked file cabinets in a locked office in an access-restricted building. A master list of names and numbers is kept in a location separate from all other study data. Only senior research staff will have access to the master list linking names and code numbers. All staff is, or will be, fully trained in relevant ethical principles and procedures, particularly around confidentiality. No personal participant information will be presented in any publication or presentations resulting from this research.

(2) Distress due to assessment procedures: To minimize the risk of distress arising from assessment procedures (interview and questionnaires), only study staff that has been adequately trained in the assessment battery will complete all assessments. Participants will also be advised that they may choose not to answer any questions that they find upsetting.

(3) Perception of coercion to participate in the study: To minimize risk of coercion, standard procedures will be followed in obtaining written informed consent. The voluntary nature of participation will be emphasized. Risks and benefits of participation will be explained, along with the rights of the

participant, including the right to withdraw from the study at any time. Additionally, participants will be informed that should they choose to withdraw from the study, this will in no way affect the care they receive at Butler Hospital or their right to participate in future research studies.

(4) MRI: The nature of the scanner environment will be explained to all participants during the consent process (i.e., you will lay on a table that slides into a narrow cylinder, you will be asked to lie still, the machine makes very loud noises, you will be provided ear protection). Participants will be informed that they may stop the study at any time by informing study staff via intercom or squeezing a safety bulb placed near or in their hand. To minimize the risk of claustrophobic reactions, participants will be screened for claustrophobia. Additionally, participants will be informed that if any heating they experience becomes uncomfortable, they should inform study staff and they may discontinue participation at any time without penalty. To reduce the possible physical risks associated with MRI, participants will be thoroughly screened by study personnel and the Brown MRI Research Facility staff prior to entering the magnetic field for the presence of any metallic objects, implants, or other safety risks, and they will have all possible risks explained to them verbally and in writing using a separate consent form at the Brown Facility. If MRI scans lead to the discovery of a previously unknown potential health problem, study staff will notify these participants as soon as possible, and appropriate recommendations will be made for further investigation by qualified medical personnel. Although the scan is not diagnostic in nature, and the study personnel and MRI technician are not qualified to make diagnoses based on imagery data, any findings warranting possible further attention will be shared with the participant and the participant will be instructed to follow-up with qualified medical personnel.

(5) CES: To minimize risks due to CES, all participants will be carefully screened for contraindications to CES as listed in the exclusion criteria. As the risks of CES during pregnancy are unknown (although most likely not harmful), pregnant individuals are excluded from participation based on historical guidelines. Use of an electrically isolated power source (i.e., battery-powered stimulation device) also protects against delivery of more intense currents than intended. Stimulation parameters (current and frequency) will be preset and tested for tolerability during Visit 1 under the guidance of Drs. [redacted]. Participants will be told that modification of the Alpha-Stim device or accessories is not allowed, and that doing so could result in injury. They will also be told to not stimulate directly on the eyes or press the probes over the carotid sinus (on the neck near the larynx) and application of the electrodes near the thorax may increase the risk of cardiac fibrillation, as well as that it is advised to not use dangerous machinery or vehicles during treatment days, and that for that reason CES should only be applied/used on off-duty days or after completion of a duty cycle. Participants will have the option of discontinuing the study at any time and will be explicitly instructed to contact the research team if they experience any discomfort. The research team will reach out to participants at least once per week during the four weeks of CES (or more often if indicated based on incomplete EMA surveys or difficulties using the CES device). To assess for presence of adverse events, we will use a recently adapted Side Effects Questionnaire based on the one developed by Brunoni and colleagues [26]. If there is any doubt about the mental or physical status of an individual during the CES intervention, participants will be evaluated by Dr. [redacted] in her role as clinical psychologist, who will make recommendations for follow-up care, if required. Telephone or in-person follow-up will be arranged as needed and will not be considered a protocol deviation. Any participant judged on clinical grounds to have suffered adverse effects will thus be evaluated and treated as necessary and withdrawn from the study if deemed necessary.

(6) EMA: Participants will be told that EMA survey reminders can be silenced to avoid interference with work-related duties, and that two reminder notifications will be sent to participants to allow completion of surveys at a later time when convenient before they expire.

(7) Oura ring: Participants will be told that if they experience skin irritation to stop wearing the Oura ring and contact the study team. Participants will also be told to be cautious that the ring does not get caught on fixed structures or heavy objects or when working with other objects that contain batteries

as this could cause a potentially dangerous electric shock.

(8) Inconvenience and burden of required time/travel: Remuneration will be offered to cover part of the subject's expenses related to participation in this research study, but subjects will not be offered reimbursement for all the expenses they may incur (e.g., gas). Butler Hospital is about a ~10-minute drive away from the Brown University MRI Research Facility, and Butler Hospital and the Brown MRI Research Facility have (dedicated, free) parking spots for participants undergoing study-related procedures/MRIs. Our experience has been that research participants generally have no difficulty accessing either location.

(9) Other: The research staff will evaluate participants prior to and post CES as well as regularly monitor participants for side-effects/adverse events during the four-weeks of CES. Dr. [redacted] is a clinical psychologist at Butler Hospital with training in and experience with neuromodulation and available to evaluate that participation continues to be safe and reasonable for participants.

Please note: **Emergencies**: If, during any study procedure, staff identifies a condition that mandates immediate clinical intervention or official reporting, all necessary steps will be taken including following local (Butler Hospital) emergency procedures.

D2. Measures to Ensure Confidentiality

Every effort to maintain participant confidentiality will be made. All research personnel will be trained in the responsible conduct of research. All study forms and data will be identified only by a unique participant ID number, and will be stored in locked file cabinets or on secure research servers or CNE REDCap. Identifying information (contact information, name, consent documents) will be separated from the research data and be stored separately in a different locked file cabinet. All computerized/digital data will be stored on a secure research server at Butler Hospital and/or University of Rhode Island, separated from identifiers. REDCap data that includes identifiers will be saved in a database separate from a database that includes only coded data. Hard copies of data capture forms, e.g., descriptive data and MRI/CES safety screening, will be kept in locked file cabinets in the Annex 3rd Floor Research Lab space at Butler Hospital. EMA data collected through LifeData is HIPAA-compliant. Data collected from the Oura ring is being securely processed through anonymization or pseudonymization of personal data, strict access control, and the use of encryption to protect the data. Oura's data privacy practices are maintained in compliance with the California Consumer Privacy Act of 2018 (CCPA) and the General Data Protection Regulation (GDPR). All data will be permanently deleted from the Oura Cloud after all data collection, data back-ups, and data analyses are completed – This only pertains to data saved with the Oura Cloud. We will retain any data obtained through the Oura ring locally at Butler Hospital. Only authorized study personnel will have access to the data. No personal participant information will be presented in any publication or presentations resulting from this research. Please note: the CES device does not generate any data. Research data will be destroyed 6 years after research study activities have been concluded.

D3. Data Safety Monitoring Plan

To meet the NIH policy for Data and Safety Monitoring, we have created a system for oversight of the project. Oversight and internal monitoring of the participants' safety will be conducted by the investigator team, given the unique expertise of each investigator. Both Drs. [redacted] have extensive experience conducting non-invasive neuromodulation in individuals presenting with a variety of (sub)clinical psychiatric symptoms, including anxiety, posttraumatic stress, and depression. Specifically, Drs. [redacted] have ongoing projects utilizing electrical current stimulation supported by the COBRE Center for Neuromodulation project and which are performed at Butler's Neuromodulation Research Facility. Dr. [redacted]., as a clinical psychologist and Director of the Study of Trauma, Risk-taking, Emotions, and Stress Symptoms (STRESS) Lab, has substantial background in the pathogenesis of posttraumatic stress disorder. Likewise, [redacted] projects mainly involve the use of non-invasive brain stimulation techniques in individuals with posttraumatic stress disorder. All participants will be carefully screened prior to study entry, and the application of and device settings for CES will be

practiced and set prior to providing the CES device to participants. Other participant safeguards with respect to study procedures are described in Protection of Human Subjects. A member of the research team will be available during working hours, and the research team will check-in with participants at least once a week. In the event of any adverse event, Dr. [redacted] as study PI will be contacted to facilitate subsequent assessment and treatment or referral as necessary.

In the event of any participant becoming unstable or demonstrating worsening of clinical symptoms during the study duration, study procedures will be stopped for this individual and Dr. [redacted] as study PI will be contacted and she will follow-up with Drs. [redacted] in their role as clinical psychologist as well as the on-call physician at the Butler Hospital TMS Clinic. In case, Dr. [redacted] is not available, the on-call physician at the Butler Hospital TMS Clinic will be contacted to facilitate treatment or referral. In case of emergency medical assistance, the study team will contact 911 and/or the Brown University EMS response team depending on severity and location (e.g., while at the Brown University MRI Research Facility). All research staff as well as MRI facility staff members at the Brown University MRI Research Facility are trained in basic first aid, CPR, and MRI safety and evacuation protocols.

To ensure the integrity of the data all data will be reviewed for errors or inaccuracy within one week after it is obtained. All data will be entered into a research database (i.e., CNE REDCap) as it is collected, and research staff will meet with the supervising co-Project Leader at least weekly or as appropriate to review ongoing subject data. Additionally, Drs. [redacted] will meet at least weekly to discuss the project, at which time they will review progress about enrollment, any adverse events, and attrition/noncompliance, review data quality, recruitment, and study retention, and examine other factors that may affect outcome. Circumstances surrounding any identified adverse events, incidents of subject dissatisfaction, or subject noncompliance or withdrawal of consent will be tracked regularly and discussed to determine any changes in participant risk.

The co-Project Leaders ([redacted] will hold primary responsibility for monitoring study safety and progress. Per IRB requirements, they will be responsible for assessing, tracking, and reporting, as necessary, any adverse events or unanticipated effects during the study to the IRB of Record (Butler Hospital). Following standard practice, serious and unexpected adverse events will be reported to the IRB of Record within the designated guidelines. For example, a serious adverse event will be reported via IRBNet within the IRB guidelines. The written report will indicate whether the serious adverse event was attributed to the study. The project Standard Operation Procedure binder will provide detailed operating procedures including the definitions of SAEs and AEs and reporting requirements. If a pattern or potential pattern of unexpected adverse events emerges during the study, Drs. [redacted] will discuss this pattern with outside physicians with expertise in brain stimulation in this population. The PI of the COBRE Center for Neuromodulation ([redacted]) will in turn be responsible for reporting safety events to the NIH.

D4. Data Management and Sharing Plan (DMSP)

N/A; proposed research is an administrative supplement to a grant (NIMGS COBRE CCN at Butler Hospital) approved for funding prior to January 25, 2023.

E. Potential Benefits

None of the assessment and experimental methods are to be diagnostic in nature or intended to treat any (mental) health condition and therefore will not be of any direct benefit to participants. However, the knowledge gained may be of potential benefit to society by starting to gain insight into whether, and how, CES might be developed as a preventative intervention for PTSD. Additionally, given that the Alpha-Stim AID CES is FDA cleared for anxiety and/or insomnia, participants who experience anxiety and/or insomnia might see a change in these symptoms.

F. Risk-Benefit Ratio

The results of this study will provide important data on whether a four-week course of CES (and related study procedures) is feasible and acceptable in active-duty firefighters. Additionally, we hope to obtain preliminary signal of changes due to cranial electrotherapy stimulation on subjective (e.g., anxiety, sleep, mood) and/or objective (e.g., neural) variables related to homeostasis. Knowing which measures might be sensitive to detect changes due to cranial electrotherapy stimulation will directly inform the design of a future, collaborative clinical trial to test efficacy of CES for the prevention of PTSD in first responders. Given the high likelihood for the development of PTSD in first responder firefighters, the benefits to knowledge to be collected with this study outweigh the risks.

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5) CRITERIA FOR WAIVER OF AUTHORIZATION FOR USE OF PROTECTED HEALTH INFORMATION (PHI)

5A. Does the requested use of PHI involve more than minimal risk to privacy?

☐ **YES** ***[if " YES," project is not eligible for PHI Waiver]*** ☒ **NO** ***[if "NO," address 1-3 below]***

1. **Plan to Protect Patient Identifiers from Improper Use and Disclosure:**
Potential risks due to loss of confidentiality will be minimized by having all information collected and handled by staff trained to deal appropriately with personal information. All research personnel will receive training in the protection of human research participants. All information will be treated as confidential information and be kept in locked filing cabinets on-site. Digitized/Computer data files will be available only to study personnel.

2. **Plan to Destroy Identifiers or Justification for Retaining Identifiers:**
After identification of potential participants and in the case (s)he does not want to participate, identifying information will be safely discarded per Butler Hospital procedures. When the person is interested in participating, identifiers will be retained so that they may be used to facilitate the research (e.g., contact participants; reimburse participants) until 6 years after completion of the study.

3. **Assurances that the PHI will not be Re-used or Disclosed:**
Information collected will be treated as confidential and only be used for the above-outlined study purposes as described (e.g., contact participants for study-related procedures). PHI collected as part of the study protocol will only be accessible to study staff. Potential participants will only be identified for the above-mentioned study.

5B. Could the research be practicably conducted without a waiver? ☐ **YES** ☒ **NO**
5C. Could the research be practicably conducted without access to and use of the PHI? ☐ **YES** ☒ **NO**
5D. Is PHI is only needed for activities preparatory to research? ☐ **YES** ☒ **NO**

DESCRIPTION OF PHI TO BE COLLECTED UNDER WAIVER

Contact and demographic information (e.g., name, phone number, date of contact) will be collected to allow the study staff to contact participants for prescreening which will inquire about basic demographic information (e.g., name, age, sex), inclusion criteria, and cursory asks about potential for CES/MRI contraindications (pregnancy, (metal) implanted devices) and ownership of a smartphone as exclusion criteria. Those meeting cursory entry criteria will be invited to participate, and an appointment date/time will be arranged at which time they will be asked to sign the consent form.

ADVERTISEMENTS

Please see the attached tear-off flyer, and social media marketing materials as a separate documents.

8) INFORMED CONSENT FORM (ICF), ASSENT OF MINOR & PARENTAL PERMISSION FORM

Indicate number of consent(s): 2
Identify each consent: Main; MRF consent addendum.