COVER PAGE – STUDY PROTOCOL

Title: Effect of tDCS Timing on Safety Memory in PTSD

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BUTLER HOSPITAL
INSTITUTIONAL REVIEW BOARD
PROTOCOL

1.) Project

Title of Project: Effect of tDCS timing on safety memory in PTSD
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Other Investigator(s): Noah Philip, MD; Nicole McLaughlin

Revision History:

Version Number	Version Date	Summary of Revisions
1.0	11/03/2018	First version
2.0	05/31/2019	1.Will enroll participants who have completed testing day 1 at the Providence VA Medical Center (PVAMC) to complete study visits 2-5. 2.Added a fear renewal phase to experimental procedures on study visit 5. 3.Update recruitment language after Butler Hospital marketing . 4.Addition of REDCap for the randomization of participants, and collection and storage of data.
3.0	10/25/2019	1.Update/broaden recruitment locations to include public areas in the greater Providence community as well as the Providence VA Medical Center (PVAMC). 2.Update language of recruitment materials to be distributed at the PVAMC. 3.Update the tDCS safety screening form to include screening for scalp conditions or damaged skin on the head, as well as obtain info on use of hormonal contraceptives and clarify questions related to neurological conditions.
4.0	03/02/2020	1.Removed references to study protocol occurring at the Providence VA Medical Center (PVAMC) or PVAMC recruited participant's having a different study procedure. 2.Removed time constraint between Visits 1 and 3. 3.Removed flyer text from protocol appendix. 4.Updated recruitment materials to be distributed at the PVAMC and VA associated locations; changes include a new photo, new language, moving the disclaimer location, and making the project title more prominent.
5.0	03/16/2020	1.Including the option to conduct baseline procedures remotely via phone/HIPAA compliant video conferencing. 2.Will allow for verbal consent for the use of e-mail to be obtained. 3.Will allow for participants to electronically provide consent. 4.Will allow for participants to electronically sign CNE paperwork. 5.Will allow research staff to send REDCap survey links to participants via email. 6.Updated the data storage options for PHI.
6.0	03/20/2020	Will allow researchers to collect additional information needed for participant safety during remote baselines.
7.0	07/08/2020	1.Added language to allow for flexibility of MRI scan on Day 2. 2.Added COVID-19 Specific Precautions. 3.Updated protocol language to account for flexibility in study location (Brown MRF and Butler Hospital.) 4.Updated electrode placements to reflect current transcranial direct current montage (tDCS). 5.Updated protocol to make Day 2 and Day 5 MRI supplemental rather than required for completion of study protocol. 6.Updated compensation to account for the optionality of the Day 2 and Day 5 MRI scans.

		7.Updated protocol to include potential risks of discomfort associated with participants being asked to wear a face mask. 8.Updated tDCS safety measures to account for tDCS procedures occurring at Butler Hospital. 9.Updated monitoring options during tDCS administration to continuously observe participants. 10.Updated online advertisement text to reflect new flexibility with Day 2 and Day 5 MRI.
8.0	08/25/2020	1.Updated recruitment methods and PHI Waiver to allow research staff to perform targeted recruiting via review of Butler Hospital medical records related to Partial Hospital Programs. 2.Submission of outreach handout to provide to potentially eligible participants. 3.Addition of a sub-study to allow data collection on the online, panel-based platform called Prolific in response to ongoing SARS-CoV-2 pandemic. This sub-study will involve the administration of questionnaires pertaining to symptoms of posttraumatic stress disorder, anxiety, and depression as well as experimental tasks assessing contextual processing. 4.Updated protocol to reflect current data storage locations.
9.0	09/08/2020	Updated recruitment language for online advertisement text to allow for two options for describing compensation.
10.0	05/12/2021	Minor increase in participant remuneration for taking part in the study.
11.0	05/28/2021	1.Updated language to account for visits not occurring in the real or simulation scanner. 2.Updated transcranial direct current stimulation language to match current procedures. 3.Updated consent procedure language to remove qualifier that the consent process will be administered in person, allowing for remote consenting. 4.Will allow for study staff, not just primary investigator, to debrief participants.
12.0	10/05/2021	Allow for text messaging.
13.0	07/07/2022	Human subject participant population to be increased from a sample of 90 participants to a sample of 150 participants who complete all study procedures. The original protocol allows for 108 participants to be collected to account for a 20% attrition rate. Therefore, to accommodate that rate, 180 participants will be recruited for a sample of 150 who complete the study tasks to be included in the final analyses.
14.0	11/15/2022	1.Clarify use of scripts and services for the online study, i.e., the use of Pavlovia to run experiments programmed in PsychoPy online, and the use of Qualtrics (Brown-license) for data collection. Psychopy collects a date-of-completion time stamp, which is considered a HIPAA identifier. 2. Limit age (in years) of online study participants to 89 to avoid data collection of age being a HIPAA identifier. 3.Update the Online Study Consent to reflect the possibility of collecting identifiable data. 4.Correct the CNE Research Application to reflect previously obtained approval for the total number of participants, i.e., we updated the “summary portion” of the application (which still read 90 participants) and the “Anticipated number of records” (which still read 150) to reflect approved number of 150 participants for the main study and 500 participants for the online study as is correctly stated in the “Proposed number of subjects to be enrolled at this site”. 5.Update CNE Research Sponsor from Dr. Garnaat to Dr. McLaughlin.
15.0	12/15/2022	Changes made to the protocol following full board review for continuing review.

16.0	12/07/2023	Changes made to Aim 4 Sub-Study

2.) Description of Study

A. Specific Aims

Aim1: Determine the temporal effects of tDCS in relation to extinction processes on extinction retention.
Prediction: Anodal tDCS targeting VMPFC immediately following extinction learning will improve extinction retention 24 hours later, compared to tDCS during extinction learning and sham stimulation.
Approach: Using a standardized Pavlovian fear conditioning paradigm, 150 participants with a diagnosis of PTSD will be randomized to receive either 1) anodal tDCS targeting the VMPFC during extinction learning, 2) similar tDCS immediately after extinction learning, or 3) sham stimulation. Extinction learning and subsequent extinction retention will be quantified by psychophysiological arousal, i.e. skin conductance responses.

Aim 2: Define temporal tDCS effects on VMPFC activity and psychophysiology during extinction retention.
Prediction: Compared to sham and tDCS during extinction, anodal tDCS after extinction will result in greater VMPFC activation during retention and correlate with associated psychophysiology. Approach: Participants will undergo fMRI during extinction retention. Imaging analyses will be used to compare groups based on VMPFC activity during extinction retention and its relationship to skin conductance responses.

Exploratory Aim 3: Evaluate whether VMPFC connectivity predicts extinction retention after tDCS.
Prediction: VMPFC to amygdala and hippocampus resting state connectivity will predict extinction retention success, most prominently for participants who received active tDCS after extinction learning.
Approach: Participants will undergo resting state functional connectivity MRI prior to fear conditioning procedures. Imaging analyses will be used to compare groups based on VMPFC to amygdala and hippocampus functional connectivity.

Aim 4 – Sub-study (online): Evaluate the impact of posttraumatic stress symptoms on contextual processing. The objective of this sub-study ("Learning and Memory in Virtual Rooms") is to test performance differences between configural and elemental contextual processing in individuals across the PTSD spectrum using an online, panel-based platform, e.g., Prolific (https://www.prolific.co/). Context plays a vital role in safety learning; whereas fear generalizes easily across contexts, learning that situations no longer need to be feared and are in fact "safe" is context-bound with limited generalization (Bouton & Bolles, 1979). Deficits in contextual processing are well-recognized in PTSD (Garfinkel et al., 2014; Liberzon et al., 2016). As such, difficulties in the recall of safety memories might not be a safety learning or memory problem, but a contextual processing problem instead. Recent research proposes that PTSD may be related to deficits in configural processing specifically, while other context-based association learning, such as elemental processing, may be spared (Stout et al., 2018). Collected data from the study will be used for further task development to design an informed research approach that allows the integration of non-invasive brain stimulation techniques. Protocol details for this sub-study are described below (starting on page 15); this sub-study has a separate consent form.

B. Background

Posttraumatic stress disorder (PTSD) is a common psychiatric disorder that occurs after exposure to a traumatic event, and is characterized by arousal symptoms, re-experiencing, avoidance, negative cognitions, and mood. PTSD is associated with significant psychiatric and medical comorbidity and health care utilization (1)(2)(3), and poor quality of life (4). Up to 7% of the U.S. population experiences PTSD over their lifetime (5) and PTSD occurs in up to 70% in specific samples of military Veterans (1, 6-7). Yet, even the most effective treatment options are often followed by relapse. Therefore, there is a pressing need to identify novel and more effective PTSD treatment options.

At its core, PTSD reflects a maladaptive fear response (8, 9), in which patients repeatedly and erroneously continue to respond to situations or events that – consciously or not – remind them of the trauma as "dangerous". Exposure-based psychotherapy aims to help patients learn that the hazardous experience (i.e., the cause of their PTSD) is no longer present or threatening in their current environment (10, 11). The extinction of conditioned fear, also called "extinction learning," is a laboratory analogue for exposure therapy and investigates how the brain forms new safety-based memories (12). Studies in humans and rodents confirm that extinction does not involve erasing or overwriting the original fear memories; instead extinction involves new learning (13-17). Thus, the goal of extinction is to form new safety memories that can be recalled to inhibit fear responses associated with the original trauma. The ability to recall new safety memories after extinction is termed "extinction retention". Abnormalities in extinction retention, and to a lesser extent in extinction learning, are extensively associated with PTSD (18-21). This corroborates observations that many patients do not adequately benefit from exposure treatment (22-24) and the majority experience symptomatic relapse in the months or years after treatment (25-27).

Neuroimaging studies broadly implicate aberrations in prefrontal-limbic neural circuitry associated with PTSD. In both human and translational animal studies of PTSD, the most commonly replicated finding is VMPFC hypoactivity (or its homologue in rodents) alongside hyperactivity in the amygdala, dorsal anterior cingulate cortex and insula as well as hippocampal abnormalities (9, 12, 28-31). VMPFC activation during extinction learning predicts extinction success, and is associated with reduction of amygdala-driven fear expression (29, 32, 33). Compared to non-PTSD control groups, individuals with PTSD show reduced VMPFC activation during fear extinction (19, 34-36). The VMPFC further plays a critical role in memory consolidation after extinction acquisition (37, 38). Memory consolidation refers to a set of neural processes that stabilize labile memories after they are acquired (39), and includes a synaptic consolidation phase that occurs in minutes to hours after learning (40, 41). The role of the VMPFC in extinction consolidation is supported by rodent studies where VMPFC blockade of calcium-dependent molecular cascades or proteins – critical mechanisms required for neurons to change synaptic connections in response to changing environments (i.e. plasticity)– immediately following extinction learning (i.e. during synaptic consolidation) impairs later extinction retention (42-44). The hypothesized role of the VMPFC in extinction consolidation is particularly relevant given that PTSD is primarily associated with extinction retention deficits, suggesting inadequate consolidation of extinction learning (e.g. 18, 19, 20).

Taken together, the evidence suggests that finding new ways to increase VMPFC activity – in the framework of extinction – is a promising approach to develop new PTSD treatments. Translational rodent studies support this notion (45, 46). The purpose of the proposed research is to determine whether the timing of transcranial direct current stimulation (tDCS) – a non-invasive brain stimulation technique – targeting the VMPFC affects extinction retention. tDCS alters cortical excitability via subthreshold modulation of neuronal resting membrane potentials using a weak constant electrical current (47, 48). Simplistically said, positive current flow (i.e., anodal stimulation) increases the likelihood of neuronal depolarization, while negative current (i.e., cathodal stimulation) may reduce this likelihood. Hence, tDCS is a truly modulatory technique that does not generate action potentials on its own but works in tandem with ongoing intrinsic neural activation. As such, tDCS biases the brain for subsequent responses to external stimuli to facilitate learning and memory processes (49), including synaptic consolidation.

Prior studies indicate that 1-2mA tDCS can impact fear memory processes (50)(51) and threat vigilance (52) in healthy controls. Yet, clinically more relevant would be to use tDCS in order to improve fear extinction learning and/or consolidation, with the goal to augment extinction retention. Previous work in our lab, indicates this is possible. However, the effects of tDCS appear to depend on the timing of stimulation in relation to extinction learning; whereas tDCS targeting the VMPFC during fear extinction improves subsequent extinction in healthy controls (53), similar tDCS applied during synaptic consolidation may boost extinction memory 24 hours later in Veterans with PTSD (54). These observations on the importance of timing are consistent with the above-mentioned VMPFC-mediated extinction consolidation deficits in PTSD and set the stage for the current study, as it suggests that the

time immediately following extinction learning, i.e. the window of synaptic consolidation, might be a particularly relevant time period for intervention to improve extinction retention in PTSD.

In this study we will use a well-validated Pavlovian learning paradigm to serve as an analogue to exposure-based treatment, which will allow for performing the critical laboratory testing prior to clinical efficacy studies. Prior research demonstrates that this Pavlovian learning paradigm correlates with exposure treatment outcomes and is a useful proxy for the processes underlying exposure (55, 56). The use of Pavlovian extinction – as opposed to exposure therapy – allows a controlled learning environment in order to directly test the effects of tDCS timing on safety memory generation and retention. Determining the optimal, i.e. most effective, stimulation timing in order to affect psychological processes underlying exposure-based treatment is of utmost importance to evaluate the potential clinical value of tDCS-augmented treatment for PTSD. The findings of the proposed research will 1) provide critical knowledge on the effects of tDCS timing to augment extinction retention, and 2) enable hypothesis driven future studies for the implementation of non-invasive brain stimulation for PTSD treatment. The ultimate goal of this line of research is to develop tDCS as an assistive device-based treatment in adjunct to existing exposure-based psychotherapeutic interventions for PTSD.

C. Experimental Method

C1. Brief Description of Subjects

Participants (N=150) will be between 18-70 years with a diagnosis of PTSD. Participants will be of any racial or ethnic group and of either sex. Participants with PTSD across trauma types (i.e. combat-related, sexual assault, accidents, etc.) will be recruited from Butler Hospital and the larger Providence metro area, including the Providence VA Medical Center (PVAMC). Although we will recruit participants across trauma types, trauma type and time since trauma will be recorded as potential variables that might affect tDCS effectivity in relation to fear extinction and recall. We anticipate including 180 participants in order to collect a sample of 150 participants who complete all study procedures.

C2. Study Design

This study will use a between-subject design, with 150 adult participants randomized to one of three group conditions (n=50 each), namely 1) receiving active tDCS during extinction learning; sham during extinction consolidation, 2) receiving sham during extinction learning; active tDCS during extinction consolidation, 3) receiving sham during extinction learning; sham during extinction consolidation. Recruitment of 50 participants per group incorporates a conservatively high 15-20% estimate of participants who may not condition while ensuring a sufficient sample size for data analyses.

This study will take place over 4 to 5 visits to Butler Hospital and the MRI Research Facility (MRF) at Brown University. It is possible for baseline procedures to be conducted remotely via phone/HIPAA compliant video conferencing. During these visits, participants will complete informed consent, screening measures, a semi-structured clinical interview, self-report questionnaires, a fear conditioning, extinction, and recall paradigm, and tDCS. Visits will vary in length between 1 to 3 hours.

Any ongoing treatment participants receive will be allowed to continue unchanged throughout the duration of the study, and should be stable for at least 6 weeks prior to start date. Participants will be asked to keep these unchanged during the study period. Treatment changes will be allowed if medically necessary.

The stimuli and experimental protocol to be used in the present study have been used extensively in previous studies examining extinction recall in human populations (19, 57-59). Furthermore, this design has been shown to reliably induce neural and behavioral responses associated with extinction memory (45). In our laboratory, this task has been well-tolerated in individuals with PTSD (53, 54).

C3. Specific Procedures or Treatments

Procedures:

COVID-19 Specific Precautions: Research staff will act in accordance with COVID-19 safety guidelines set by the Brown MRF and Butler Hospital.

Prescreening. Interested individuals will be provided 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, and whether they have ever been a patient at Butler Hospital. Inclusion and exclusion criteria may be verified by inspection of the medical record as part of the prescreening process for individuals who have expressed interest in participating (see PHI Waiver below). Those meeting entry criteria will be invited to participate and an appointment date/time will be arranged; additionally, verbal consent for the use of e-mail will be obtained.

Visit Day 1: Screening. May occur remotely over the phone/via HIPAA compliant video conferencing or in-person at Butler Hospital. At the time of appointment, individuals will be presented with the Informed Consent Form and given a verbal explanation of the study procedures, risks and benefits, as well as given the opportunity to ask additional questions. For participants who electronically provide consent, the consent will be reviewed again at the time of the first in-person visit. After signing the Informed Consent Form, participants will undergo further screening consisting of collection of demographic and clinical information (e.g., age, gender, racial/ethnic group, handedness, years of education, use of medication and current treatments, colorblindness, menstrual cycle or use of hormonal contraceptives if female) and further assessment of tDCS/MRI contraindications, see Appendix. For remote baselines, additional information such as the participant's current location and the privacy and safety of said location will be obtained. This is to assist the research team in case suicidal intent is endorsed and study clinician intervention or emergency services are required.

Participants will also complete:

- A semi-structured clinical interview with a trained evaluator to assess psychiatric diagnoses and inclusion/exclusion criteria, which will include either the Structured Clinical Interview for DSM-5 (SCID-5) (60) or the Mini International Neuropsychiatric Interview (61),
- the Clinician Administered PTSD Scale (CAPS) (62) which is a 30-item structured interview to assess the 20 DSM-5 PTSD symptoms, questions target the onset and duration of symptoms, subjective distress, impact of symptoms on social and occupational functioning. The CAPS is considered the gold standard in PTSD assessment,
- Inventory of Depressive Symptoms, Self-Report (IDS-SR) (63) is a 30 item self-report questionnaire on depression severity with a Cronbach's α ranged around 0.80-0.93.
- the PTSD Checklist (PCL-5) (64), which is a 20-item self-report measure that assesses severity of the 20 DSM-5 symptoms of PTSD,
- the Pittsburgh Sleep Quality Index (PSQI) (65) to assess quality of sleep. This scale includes 19 individual items to generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction,
- the Positive and Negative Affect Schedule (PANAS) (66) is a 20-item questionnaire to evaluate general affective status and mood. Ten questions inquire about negative mood states, and the other 10 questions cover positive mood states,
- the State-Trait Anxiety Scale (STAI) (67) to evaluate self-report symptoms of anxiety outside of PTSD symptoms. The STAI contains 20 items for assessing trait anxiety and 20 for state anxiety. State anxiety items include: "I am tense; I am worried" and "I feel calm; I feel secure." Trait anxiety items include: "I worry too much over something that really doesn't matter" and "I am content; I am a steady person." All items are rated on a 4-point scale (e.g., from "Almost Never" to "Almost Always"). Higher scores indicate greater anxiety. Internal consistency coefficients for the scale have ranged from .86 to .95; test-retest reliability coefficients have ranged from .65 to .75

Individuals deemed eligible for the study will be randomized to 1) receiving active tDCS during extinction learning; sham during extinction consolidation, 2) receiving sham during extinction learning; active tDCS during extinction consolidation, 3) receiving sham during extinction learning; sham during extinction consolidation.

Visit Day 2: MRI. Participants may be asked to complete an MRI screening form and a resting state functional MRI scan, described below under MRI in further detail. Expected duration of Visit Day 2 is 1 hour.

Visit Day 3: Habituation and Fear Conditioning. On visit 3, participants will be asked to complete habituation and fear conditioning phases of the fear conditioning, extinction, and recall paradigm (18, 19, 45, 53, 54, 57). This task involves the computerized presentation of photographs of two different rooms, one serving as the fear acquisition context (CX+; picture of an office) and one as the fear extinction context (CX-; picture of a bookcase) in which two conditioned stimuli (CS+; red and blue light) and one never-to-be conditioned stimulus (CS-; yellow light) will be presented. One CS+ will be extinguished during extinction (CS+E) and the other will not (CS+U). See Figure above at right. Experimental scripts will run in E-Prime, and for all trials during each of four task phases - habituation, conditioning, extinction learning and extinction retention - the CX (+/-) will be presented for 9s: 3s alone, followed by 6s in combination with the CS (+/-) with a 15s average inter-trial interval (12-18s). During each of the four task phases two electrodes will be placed over the second digits of the index and middle fingers of the dominant hand, which may or may not deliver an annoying, but non-harmful electrical shock acting as unpleasant, unconditioned stimulus (US). Before each task phase, except habituation, participants will be instructed that they "may or may not be shocked," and to "pay attention to any patterns you observe between the image that you see and whether or not it is followed by a shock," Participants will also be instructed that "if you observe a pattern, it will hold throughout the session and the rest of the experiment." Participants will not be explicitly informed of the CS/US contingency.

Prior to starting habituation, participants will individually select electric shock intensity to be ''highly annoying but not painful" as the US, following previously used procedures in our lab (53, 54). During habituation participants will be told that the purpose of this phase is to familiarize them with all possible pictures in the experiment, and that no shock would be delivered. Participants will see all stimuli (i.e. to-be CS+E, CS+U, CS-) once in both contexts (CX+ and CX-). After habituation participants will undergo fear conditioning. A total of 32 trials: eight CS+E, eight CS+U, and 16 CS- trials will be presented across two blocks in the CX+ only. Both CS+ trials will be paired with US at a 60% reinforcement rate. The US will occur immediately after CS+ offset. After fear conditioning, participants will complete contingency ratings and the PANAS to assess general affect. Habituation and fear conditioning will either occur at Butler Hospital or in the simulation scanner at the MRF. This visit will last approximately one hour.

Visit Day 4: Extinction of Conditioned Fear. Visit 4 will need to occur 24 hours after visit 3, with an allowable deviation of 4 hours. Extinction learning will either occur at Butler Hospital or in the simulation scanner at the MRF. Participants will be reminded of the instructions and receive either 1) active tDCS during extinction learning, or 2) active tDCS immediately following extinction learning, or 3) sham stimulation according to the randomization schedule. Regardless of randomization group, all participants will be asked to repeat completion of Day 1 tDCS safety screening and tDCS equipment will be placed on the scalp before beginning the task. During the extinction phase a total of 12 trials: six CS+E and six CS- trials will be presented solely in the CX- and no shocks will be delivered. Median split will determine the latter three CS+E trials as 'late extinction' trials. After extinction and tDCS procedures, participants will complete contingency ratings and the PANAS to assess general affect. This visit will last approximately one hour.

Day 5: Extinction Retention and Fear Renewal. Visit 5 will need to occur 24 hours after visit 4, with an allowable deviation of 4 hours. The extinction retention and renewal phases serve as the test phase and

will either be administered at Butler Hospital or in the real MRI scanner at the Brown MRF. Prior to starting extinction retention, participants will be reminded of the instructions. A total of 32 trials: eight CS+E, eight CS+U, and 16 CS- trials within the CX- only will be presented and no shocks will be delivered. Early recall retention will be based on the first four CS+E and first four CS+U trials. After extinction retention, participants will complete contingency ratings and undergo a fear renewal phase. During fear renewal participants will see the same content as during fear conditioning, but no finger shocks will be delivered. After fear renewal participants will complete contingency ratings and the PANAS to assess general affect. This visit will last approximately one hour.

Skin Conductance. Skin conductance will be recorded for 2 minutes prior to each fear conditioning, extinction and recall phase to establish a physiologic baseline, and continuously throughout each phase. Baseline skin conductance level will be used as a covariate in analysis. To assess skin conductance, two MRI-compatible electrodes will be placed on the thenar eminence of the non-dominant hand, as we will be assessing skin conductance in both the simulator and real scanner depending on task phase as described above. Skin conductance reactivity (SCR) will be quantified by the phasic response that occurs after the presentation onset of each CS+/- stimulus following previous guidelines (57) and our prior work (53, 54). The first trial during fear conditioning will be removed from analyses to avoid the influence of an orienting response on the data. Because of the effects of nicotine and caffeine on SCR we will ask people not to consume nicotine or caffeine two hours prior to the start of the study.

Transcranial direct current stimulation. *Device*: Continuous direct current stimulation will be delivered by a CE-certified tDCS device (NeuroConn).
tDCS Electrode Montage: We will use a conventional 1 (anode) x 1 (cathode) midline bipolar-non balanced electrode montage (68) with the anode placed approximately over FP1 of the 10-20 EEG coordinate system and the cathode over P10.
Rationale: To determine the ideal electrode montage, participants will undergo a structural MRI scan (with acquisition settings optimized for modeling inputs) on Day 2 to inform finite element modeling (69). Initial electrical field modeling of the proposed montage was obtained using tDCS Explore by Soterix Medical (v.4.0, New York, NY). This modeling will be confirmed based on individual neuroanatomy MRI scans obtained on Day 1 using SimNIBS software (v2.0, DMCR, Germany) and electrode montage will be adjusted as necessary in collaboration with the Neuroimaging and Neuromodulation Core. Electrodes will be placed at FP1 and P10 and might be adjusted (by Drs. van 't Wout-Frank and Philip) based on the latter individualized modeling to target VMPFC region. Using this approach, we anticipate at least 0.25-0.35 V/m will reach the VMPFC. Prior tDCS research has demonstrated that tDCS effects in this order of magnitude have effects on brain functioning (70).
Dose Parameters: Active tDCS will consist of approximately 15 minutes 2 mA intensity through 3x3 cm (9 cm^2) or 5x5 cm (25 cm^2) electrodes, resulting in a maximum 2.22 A/m2 current density, with an additional 30s ramp up/down at the beginning and end of stimulation, respectively. Active tDCS will be applied either during extinction learning or immediately after extinction learning. This duration is selected based on task duration and allows an additional 2 minutes of tDCS prior to the start of extinction learning. Sham stimulation will be applied for the remainder, namely after or during extinction learning respectively. Sham stimulation parameters – 1 mA for 30s, with a ramp up/down over 30 sec each – are selected to mimic the scalp sensation of active tDCS without prolonged intense stimulation.
Rationale: 2 mA intensity was chosen based on research showing that more intense stimulation protocols may result in stronger effects on the brain (71) and cognition (72).

Transcranial direct current stimulation Procedures: Two conductive rubber electrodes will be inserted into reusable sponge pockets saturated with 0.9% normal saline and securely attached to the participant's scalp using a rubber headband prior to beginning the task on Day 4. To reduce the likelihood of side effects, the skin under the stimulation sites will be lightly cleaned with alcohol and inspected for lesions or abnormalities. Participants will be instructed to notify the experimenter of any discomfort. To ensure tDCS tolerability and condition the skin, all participants will receive brief stimulation (1 mA for 30

seconds, with a ramp up/down over 30 seconds each) prior to beginning the task. Impedance, indicating electrode contact quality, will be monitored and recorded throughout tDCS administration. tDCS (or sham) will start 2 minutes prior to extinction learning and will continue throughout the extinction learning phase. For participants randomized to tDCS after extinction learning, tDCS will start immediately after completion of the last extinction trial. We will evaluate tDCS tolerability and adequacy of blinding following task procedures on Day 4. Double-blinding of sessions (active vs. sham) will be achieved through the use of participant-specific blinding codes preset in the tDCS device. Dr. Philip (mentor) will generate and oversee unblinded codes. Side effects related to tDCS will be recorded using a tDCS side effects questionnaire, including but not limited to queries about skin discomfort, headache and dizziness based on Brunoni et al. (73), see Appendix.

MRI Procedures and Data Acquisition. MRI data may be collected on Day 2 and/or Day 5 of the protocol. The decision to have participants complete a Day 2 and/or Day 5 scan will be made at the discretion of the PI. Scans will be obtained using a research-dedicated 3T Siemens Prisma MRI scanner housed at the Brown University MRI Facility. During the MRI(s), participants will lay in a supine position inside the magnet bore with head resting inside a Siemens 64 channel head coil. To minimize motion artifact, foam wedges will be used to stabilize the participant's head and a large cushion will be placed under the knees. Potential Day 2 scans will consist of a structural scan, followed by a resting state functional connectivity scan, and Diffusion Tensor Imaging. Potential Day 5 scans will consist of a structural scan, followed by a resting state functional connectivity scan, and fMRI during extinction recall and fear renewal phases. The simulation scanner is located in a room next to the active MRI scanner. For both the real and simulation scanner, visual stimuli during experimental task phases will be back projected onto a screen and viewed through a mirror attached to the head coil. Dr. Philip (mentor) will provide oversight for MRI data acquisition. If procedures take place at Butler Hospital, i.e. no Day 5 MRI scan, visual stimuli during all experimental task phases will be displayed on a computer screen in front of the participant.

All MRI images will be obtained during a 45-55 minute scan session. The first 15 minutes will be used to familiarize the participant with imaging procedures, re-assess for pregnancy if indicated, and move the participant into the magnet bore. This will be followed by acquisition of high-resolution anatomic images and functional multiband echoplanar (MB-EPI) images. Freesurfer-preferred multiecho MPRAGE protocol will capture anatomic images (e.g., FOV: 256 mm, 176 sagittal slices, slice thickness 1 mm, phase encoding anterior-posterior; TR 20ms, TE 1.85+n2.0 ms (where n = 0,..,7)). Twelve minutes of resting state data will be obtained while participants view a light fixation cross against a black background (TR = 1 ms, TE = 30 ms, FOV = 192mm, 2mm isotropic, multiband factor=4).

C4. Data Analysis

The PI(s) will be responsible for and supervise data collection and data management. Data will be stored in password-protected excel files. Data analysis will be conducted using SPSS. Data will be analyzed through linear models including (M)ANOVA, repeated measures analyses and linear mixed model procedures to deal with correlational and order effects. This will be followed by appropriate post-hoc analyses comparing specific conditions (e.g. tDCS vs sham stimulation and CS+E, CS-U, CS-). In order to maintain anonymity in SPSS files participants will be only 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.

This study will use Care New England's instance of REDCap for electronic consenting, obtaining signatures for relevant CNE paperwork, the randomization of participants, and 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. Surveys, the informed consent, CNE paperwork, etc. may be sent to participants via REDCap. They will receive an e-mail from a study email address containing a link, which will securely connect them directly to the REDCap system. A copy of the informed consent form will be sent to the participant via email following their e-consent. With regards to email communication, all emails will be sent via a secure, encrypted system.

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/.

D. Material Inducements

Compensation will be offered for the study-related procedures administered in this study. For participants recruited through Butler Hospital, and who complete all four study visits under the Butler protocol, participants will receive $50 for Visit Day 1 and $40 for Visit Days 3-5, respectively, totaling to $170 for all four testing days. In addition, participants will receive an additional $50 for each MRI they are asked to complete (Day 2 MRI and/or Day 5 MRI). This would then total to $220 for completion of one scan or $270 for completion of two scans. Study payment will occur at the end of each visit. If participants are deemed ineligible after screening on Visit Day 1 they will receive $50. If participants withdraw from the study before completion - either because they terminate consent or the study team decides that study continuation might be unsafe - they will receive compensation up until what was completed, at minimum $50 (study visit 1 only), plus $10 for each full half hour they participated (study visits 2-5).

Compensation will be in the form of checks or gift cards. If participants opt for compensation through checks we will need to collect additional sensitive data (e.g. bank account number and participant home address).

E. Training of Research Personnel

All research personnel will be trained to properly administer the study protocol by the PI. tDCS will only be applied under supervision of the PI, who is trained in its administration. 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 150 individuals with a diagnosis of PTSD and will be of any race, ethnic group or sex. Only participants who are able to give fully informed voluntary written consent will be accepted. Participants who enter will be free to withdraw from the study at any time without penalty or compensation for their time. They will be at minimum 18 years old and maximum 70 years old.

Inclusion criteria are as follows:
(1) Primary diagnosis of PTSD, assessed by the Structured Clinical Interview of DSM-5 (SCID);
(2) aged 18-70;

(3) ability to speak, read, write, and understand English sufficiently well to complete study procedures and provide informed consent;
(4) Stable psychiatric medication use or treatment for at least 6 weeks.

Exclusion criteria are as follows:
(1) Lifetime history of psychotic or bipolar disorder;
(2) Current moderate or severe substance use disorder; if mild, not under the influence at time of study participation;
(3) Acute suicidal or homicidal ideation as detected on screening instruments or in the investigator team's opinion, is likely to attempt suicide within 6 months;
(4) current (or past) significant neurological disorder, injury, or other intracranial pathology including severe traumatic brain injury or lifetime history of a) seizure disorder b) primary or secondary CNS tumors c) stroke or d) cerebral aneurysm;
(5) lifetime history of moderate or, current unstable medical conditions;
(6) Any problems that would interfere with study participation, including MRI- or tDCS-related contraindications (e.g., implanted metallic devices/substances, metallic tattoos, pregnancy, claustrophobia, holes in the skull, skin abnormalities under stimulation sites), or indication of colorblindness, or presence of any other condition or circumstance that, in the opinion of the investigator team, has the potential to prevent study completion and/or inability to schedule visit days within allotted time, and/or to have a confounding effect on outcome assessments.

B. Recruitment and Consent Procedures

Recruitment will primarily take place through the posting of advertisements onsite at Butler Hospital, online (e.g., Craigslist, Butler Hospital website, etc.), and in the larger Providence community including, but not limited to, local coffee shops and the Providence VA Medical Center*. Potential participants from Butler Hospital clinics/partial hospital programs (e.g., Partial Hospital Programs/Women's Partial Program) may be identified from review of medical records. These potential participants will be contacted using an outreach handout to determine whether or not they consent to being contacted for more information. Individuals who inquire about participation will be contacted by study staff, provided with a brief verbal description of the study, and invited to participate if they appear eligible based on pre-screening. At the time of the first study visit, potential participants will again be provided with a description of the study and if they remain interested, study staff will obtain written informed consent either in-person or via REDCap. The consent process will be administered by a member the study team who has received training in the protection of human research participants. Participants will be given the opportunity to ask any questions they may have, and they will receive a copy of the informed consent document including contact information, should any questions or concerns arise at a later time. If the participant has electronically signed the consent form, research staff will review the consent again at the first in-person visit prior to beginning other study procedures. For individuals who do not have a medical record at Butler Hospital, one will be created at time of enrollment into the study, after having signed the appropriate Butler Hospital informed consent form. Participants will be made aware of this procedure at time of pre-screening as well as through the informed consent form.

*The following text is mandatory for advertising on the Providence VA Medical Center campus: "This announcement is for informational purposes only. This study: is not affiliated with or conducted by the PVAMC, has not been reviewed by the VA's Institutional Review Board, and is not endorsed by the VA. The VA is not responsible for any costs incurred by a Veteran participating in this study." This disclaimer will only be added to the recruitment materials that will be distributed at PVAMC, see examples attached.

C. Potential Risks

Potential risks to all subjects include:
(1) Coercion. Subjects may feel coerced to participate.

(2) 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.
(3) Distress due to assessment procedures. Asking participants about their thoughts, feelings, behaviors, and symptoms during the interviews and completion of rating scales might increase distress or result in discomfort. Participants may experience physical discomfort when asked to wear a face mask or may feel uncomfortable at their inability to see the facial expressions of research staff wearing face masks.
(4) Risk related to fear conditioning, extinction and recall paradigm. The electric shocks that participants will receive during the extinction recall task may be uncomfortable, but they should not be painful or dangerous. Level of shock is personally determined by the participant to an intensity that is "very annoying but not painful." Participants are free to stop the experiment at any time, should any portion prove too uncomfortable. There is also a risk of distress associated with testing, especially from receiving shocks.
(5) Risks related to tDCS. Although tDCS is considered a low risk technique that is well tolerated and carries minimal to no side effects, there is some inherent risk with the application of electrical current. Stimulation is frequently accompanied by an itchy or prickly sensation on the skull under the electrodes. The most common side effects include mild local sensations at the electrode sites, including tingling or itching, and moderate fatigue, headache, and temporary redness of the skin under the electrodes (74, 75). Skin irritations can occur and, in a small number of case reports, local skin burns where the electrodes are attached have been reported. In addition, we are aware of reports of a small percentage of patients developing temporary hypomania during the course of a daily tDCS protocol for depression targeting the dorsolateral prefrontal cortex. It is unclear whether this is a risk for tDCS with the electrode montage used in this study, targeting a different brain region and occurring only in a single session. In research experience totaling 567 tDCS sessions, Poreisz and colleagues reported that no participants requested tDCS be stopped or required any medical intervention during or after stimulation (75).
(6) Risk related to MRI. The bore of an MRI scanner, whether it is the actual scanner or the simulation 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 in close proximity to the magnet. 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.
(7) Risks related to e-mail communication. There are risks associated with sending health information via e-mail. There is always a risk that the message could be intercepted or sent to the wrong e-mail address. E-mail messages from research staff may contain health information that identifies the participant. Information sent by e-mail could allow others to identify the participant along with their medical health conditions and psychiatric diagnosis (if applicable). Only the research team will have access to e-mail communications. We will only communicate by e-mail to send the participant information listed in the consent form. We will not send e-mail messages that contain urgent information or results of medical tests or diagnostic procedures. We will not send messages that direct the participant to get medical care.
(8) Risks related to text messaging. There is always a risk that a text message could be intercepted or sent to the wrong number. Only the research team will have access to text message communications. We will only communicate by text message to send the participant information listed in the consent form. We will not send text messages that contain urgent information or results of medical tests or diagnostic procedures. We will not send messages that direct the participant to get medical care.

D. Protection of the Subject

D1. Measures to Minimize Potential Risks

Participants can take breaks when needed during their participation. Participants will be told they may stop participating in the study at any time should. They will be informed that they may refuse to answer any questions during the study.

(1) 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 care they receive at Butler Hospital or their right to participate in future research studies. Electronically signed consents will be reviewed with research staff prior to beginning in person study procedures.
(2) To minimize risk of breach of confidentiality or loss of privacy, procedures outline below under "D2. Measures to Ensure Confidentiality" will be followed.
(3) 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. Individuals will also be advised that they may choose not to answer any question that they find upsetting.
(4) Management of risks associated with the fear conditioning, extinction and recall task. The aversive stimuli in the fear conditioning, extinction and recall task (annoying shocks) are presented using standard laboratory equipment, which have been extensively used in human studies and have been well tolerated. We will closely monitor participants for untoward reactions or distress and modify or terminate the tasks as needed to minimize any distress they experience. Participants may choose to stop the task at any point. Also, all participants will be debriefed by study staff after completing the study, at which time they will be encouraged to ask questions and discuss any discomfort that they felt at any time during the study.
(5) Management of risks due to tDCS. All participants will be carefully screened prior to tDCS for contraindications to tDCS (see exclusion criteria, e.g. as the risks of tDCS in pregnant women are unknown, pregnant and breastfeeding women are excluded from participation). Participants will have the option of discontinuing the study at any time and will be explicitly instructed to inform the tDCS administrator/PI immediately if they experience any discomfort. All tDCS will be administered, according to tDCS device instructions, by a trained member of the research staff, under the supervision of the PI.

Regarding tDCS device instructions, the use of an electrically isolated power source (i.e., battery-powered DC stimulation device) protects against delivery of more intense currents than intended. These devices also feature a continuous visual indication of electrode contact quality during all phases, a clear indication of the actual current supplied at time of stimulation, and the ability to deliver sham stimulation for single and double-blind studies. Prior to active or sham tDCS, participants will be primed for stimulation by applying a 1 mA stimulation for 30 sec, with a ramp up/down over 30 sec each. Impedance of tDCS will be recorded and monitored throughout the session to be below 25 kΩ (which is well below the pre-determined factory device maximum of 55 kΩ). The proposed stimulation is within the typical range of intensity (1-2mA) and duration (up to 20 min) for tDCS administration. No serious adverse side effects have been reported in previous studies within our lab with the proposed stimulation settings. Prolonged passage of direct current across metallic electrodes (where electrons from the stimulator are converted to ions carried through the body) can produce undesired electrochemical products such as pH changes. Electrodes will be embedded into a specifically designed sponge pad moistened with normal, 0.9% saline which will act to physically separate, and thus buffer, the skin from electrochemical changes and maintain even current density over time.

Given our proposed stimulation parameters, the proposed tDCS protocol is considered conventional in that it meets current, duration and charge safety limits. In tDCS safety testing, subjects were exposed to current densities of up to 2.56 mA/cm2, and durations of up to 22 minutes. No burns or significant discomfort occurred. In addition, electrodes will not be placed over skin lesions, such as vascular moles and angiomas that might have greater conductance than the surrounding skin, and the skin under the electrodes will not be abraded prior to stimulation. The safety of conventional tDCS has been recently published in a review by Bikson et al. (74). In the numerous tDCS studies performed in recent years, tDCS was associated most commonly with a mild tingling sensation (70.6% of 567 tDCS sessions in 102 subjects), moderate fatigue (35.3%), and a light itching sensation under the stimulation electrodes (30.4%). Headache (11.8%), nausea (2.9%) and insomnia (0.98%) were also reported, but fairly

infrequently (75). However, the most serious adverse effect of tDCS consists of the formation of small circular skin burns under the electrodes (76-78). These studies have demonstrated that the risk for skin burns increases when the skin under the electrodes is vigorously abraded before stimulation (Loo et al., 2011) or tDCS is applied without an adequate skin buffer during multiple, consecutive tDCS sessions. Subsequent tDCS practices in which the skin was not abraded before stimulation and the use of sodium chloride solution or gel, together with replacement of deteriorated tDCS supplies (e.g. sponge pads or electrodes) have not resulted in skin burns. Hence, in this study we will 1) not abrade any skin before tDCS application, 2) always use normal saline to moisten the tDCS sponges in which electrodes are embedded, and 3) carefully inspect the electrodes and electrode holders for damage or wearing. In addition, given the reported case studies of hypomania in a course of daily tDCS application, we exclude participants with a history of bipolar disorder.

Other precautions will consist of instructing participants to inform the experimenters of any (increasing) discomfort during testing (as such discomfort may be an indication that skin burns could form with continued stimulation), inspection of stimulation sites as needed and immediate discontinuing stimulation if discomfort occurs. Instantaneously making or breaking of the stimulating circuit results in AC current transients that cause neuronal firing (47). This is noticeable as brief retinal phosphenes with electrodes near the eyes. Therefore, participants will be told in advance that if the tDCS stimulator needs to be turned off suddenly out of safety precautions, they may experience a one-time sensation of a brief light flicker (similar to a broken fluorescent light) due to the sudden offset of the device.

To assess for presence and tolerability of adverse events, we will use the tDCS Adverse Effects Questionnaire, developed by Brunoni and colleagues (73). For tDCS procedures occurring at the Brown MRF, the principal investigator will be present in the room for the first five participants and onsite for future participants. For tDCS procedures occurring at Butler Hospital, physician with advanced training in Neuromodulation techniques will be immediately available for management of emerging events. Dr. Philip, in the role as study physician/mentor, will also be available to supervise or consult on tDCS administration and will be available to consult on handling of any emergent events. If there is any doubt about the mental or physical status of an individual after testing, the supervising physician will be called to evaluate the participant and make a recommendation for follow-up care if that is required.

Prior to administering tDCS in this protocol, all staff involved in administration of tDCS will be required to undergo training and demonstrate competence in the safe delivery of tDCS. There are multiple components of training in order to be able to administer tDCS, including initial *didactic training* to introduce concepts critical to tDCS, direct *observation* of tDCS procedures, *practice* of the various steps of setting up/administering tDCS on non-patient volunteers, including role-plays of scenarios of when the covering physician should be consulted to further address adverse events related to the study protocol, and *demonstration of competency* in all aspects of relevant subject assessment and in administration of the entire tDCS procedure under direct observation of a qualified tDCS administrator.

tDCS will be administered by the tDCS Operator (Dr. van 't Wout-Frank or the research assistant (TBD)). The tDCS Operator is trained in the use of tDCS devices and has knowledge of safety considerations and precautions associated with tDCS. Responsibilities include of the tDCS Operator include:
A) Positioning or assessment of positioning of the tDCS device on the participant prior to initiating stimulation.
B) Operation of or monitoring of the hardware associated with the tDCS device.
C) Administration of tDCS, or monitoring thereof.
D) Brief assessment of relevant mental status and general clinical condition before and after tDCS.
E) Monitoring of the participant during the tDCS session. The tDCS Operator will either remain in the testing room, use direct in-between room video feed, or between-room windows, to allow continuous observation of the participant's physical status for the potential occurrence of adverse events throughout the entire tDCS session.

F) Making routine adjustments to the placement of the device as required and consistent with product labeling (e.g., to ensure contact between participant's head and electrode) during the tDCS session.
G) Determination of circumstances under which tDCS should be interrupted or terminated (e.g., participants expresses increasing comfortableness under the electrodes; observation of participants for signs of skin burns, discomfort or other stress; participant wants to discontinue study procedures).
H) Taking action in accordance with established regulations in case of adverse events, e.g. contacting Neuromodulation Facility Attending Physician, reporting adverse events to PI (who will take appropriate action, as required).

(6) Minimization of risks associated with MRI: The nature of the scanner environment – real or simulation – 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 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. In the event that 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.

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 and the Principal Investigator will be responsible for ensuring that adequate training has been completed. All study forms and data will be identified only by code numbers, and will be stored in locked file cabinets or on secure research servers. 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 data will be stored on a secure research server (COBREresearch server) in password-protected files, separated from identifiers. Hard copies of data capture forms, e.g. descriptive data and tDCS safety screening, will be kept in locked file cabinets in the Annex 3rd Floor Research Lab space at Butler Hospital to which only authorized study personnel will have access. No personal participant information will be presented in any publication or presentations resulting from this research.

Please note: the tDCS device does not generate any data besides a display notification of contact quality of the electrodes. This contact quality notification is recorded for analysis on de-identified hardcopy data capture forms.

D3. Data Safety Monitoring Plan

In order 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 Dr. van 't Wout-Frank in collaboration with Dr. Philip (mentor). Dr. van 't Wout-Frank has extensive experience conducting non-invasive neuromodulation, especially transcranial direct current stimulation, in both healthy volunteers as well as individuals diagnosed with posttraumatic stress disorder. All participants will be carefully screened prior to study entry. tDCS will be administered by a tDCS-trained research team member. Other participant safeguards with respect to study procedures are described in Protection of

Human Subjects (e.g.: use of electrically isolated power source, close observation for signs of skin burns, discomfort, or other stress, explicit instruction that participants can discontinue the study at any time, etc). A member of the research team will be on-site during all study sessions, and in the event of any adverse event, Dr. van 't Wout-Frank and/or the study physician (e.g. Dr. Philip, MD) will assess the subject and facilitate subsequent treatment or referral. In the event of any subject becoming unstable or demonstrating worsening of clinical symptoms, the principal investigator and/or their designee will stop study procedures and contact Dr. van 't Wout-Frank for assessment and to facilitate treatment or referral. In case for need of emergency medical assistance, the principal investigator and/or their designee will contact 911 and/or Brown University EMS response team depending on severity. All research staff performing tDCS as well as MRI facility staff members at the Brown University MRI Research Facility are trained in basic first aid, CPR, and tDCS and/or MRI safety and evacuation protocols. All members of the research team will have 24-hour access to investigators or study physician for management of any clinical emergency that may arise.

To ensure the integrity of the data the PI will review all the data for errors or inaccuracy within one week after it is obtained. All data will be entered into a research database as it is collected, and the research assistant(s) and postdoctoral research associate will meet with the PI weekly or as appropriate to review ongoing subject data. The PI and mentor(s) will meet weekly to discuss the project, at which time they will review progress with regard to 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.

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 by fax or e-mail within 1 business day, followed by a written report within 5 days. They will be reported verbally to NIH within 24 hours and in a written report within 72 hours to both NIH and the Data Safety and Monitoring Board (DSMB; see below). The written report will indicate whether the serious adverse event was attributed to the study. A summary of adverse and serious adverse events will be reported in the yearly progress report to NIH. The project Standard Operation Procedure binder will provide detailed operating procedures including the definitions of SAE's and AE's and reporting requirements. If a pattern or potential pattern of unexpected adverse events emerges during the course of the study, the PI and mentor(s) will discuss this pattern with physicians with expertise in brain stimulation in this population as part of the DSMB described below.

The DSMB will be comprised of mental health providers and physicians who have many years of clinical and/or clinical research experience and are well versed in the protection of confidentiality. The DSMB will meet twice per year to evaluate progress, and review data quality, recruitment, study retention, adverse events, and other factors that may affect outcome. These data will be provided by the PIs to the Board. A brief report will be generated for the study record and forwarded to the Institutional Review Board as necessary. The Investigators and DSMB will be available to meet outside of the regularly scheduled meetings, as needed, if concerns regarding a particular participant or any problems arise. If necessary, they will make appropriate recommendations for changes in the protocol. The Data and Safety Monitoring Board will review all adverse events and serious or unexpected adverse events and provide recommendations. Participants will only be identified by number during review of study progress by the DSMB. In the event that confidentiality must be breached (e.g., suicidal/homicidal ideation or attempt), only the PI would be informed of identifying information in order to report to the DSMB, appropriate authorities or health care providers. In the event that a conflict of interest within the DSMB is identified, the DSMB will disclose the matter to the involved institutions and NIH. The PI will consider the recommendation and make a decision and document the action to the involved institutions and NIH. We

will inform NIH of any significant action taken as a result of the Data and Safety Monitoring Board's findings.

E. Potential Benefits

There are no direct benefits to participants for participating in the study. Indirectly, participants will be helping to further scientific knowledge with the ultimate goal to improve mental health therapy.

F. Risk-Benefit Ratio

It is our opinion that the benefits of furthering our knowledge of the effects of tDCS timing on fear extinction learning and memory can provide greater insight in the ultimate potential use of tDCS as a clinical treatment option for PTSD and related disorders. Therefore we believe that the benefit of this study outweighs the potential risks that may occur as a result of participating in this study.

Aim 4 – SUB-STUDY (online): "Learning and Memory In Virtual Rooms"; Contextual processing along the PTSD spectrum

In order to address Aim 4 and evaluate the impact of posttraumatic stress symptoms on contextual processing, we include the following online-only sub-study.

Following a within-subjects study design, up to 500 adult participants, between 18 and 89 years, will be asked to complete experimental tasks that assesses configural and elemental contextual learning and memory. The 89-year age cut-off is used to avoid data collection of age being a HIPAA identifier. For example, participants will see different images of virtual rooms that include arrangements of common household furniture (e.g., couch, table, rug, plant). Over time participants will learn that certain objects (e.g., plant) or furniture configurations (e.g., white couch on left plus plant in foreground) are associated with the presence of a "bomb" in specific rooms by showing them an image of an explosion on the next screen. After learning, contingency ratings will be obtained by asking participants whether they think a bomb is present in various virtual rooms and how certain they are on a sliding scale.

Participants will also be asked to state their age (in years), sex assigned at birth (male/female), and complete questionnaires assessing the presence of symptoms related to PTSD (e.g., PTSD Checklist for DSM-5 (PCL-5)), depression (e.g., Patient Health Questionnaire depression scale (PHQ-8)), and anxiety (e.g., Generalized Anxiety Disorder 7-item scale (GAD-7)). Additionally, random attention checks using "catch" items will be included throughout the experiment. An example of such an item is "Please select 'yellow' out of the following options: a) yellow, b) blue, c) red, d) green."

It should be noted that we will not be able to review answers to questions in real-time. As such, we are not able to detect participants who might be at (higher) risk for self-harm. For that reason, we will list the phone number and URL for SAMHSA's National Helpline – 1-800-662-HELP (4357) and https://www.samhsa.gov/find-help/national-helpline – at the bottom of each page when participants are completing the above-listed questionnaires as well as at the end of the study on a thank you-page. SAMHSA is "a free, confidential, 24/7, 365-day-a-year treatment referral and information service (in English and Spanish) for individuals and families facing mental and/or substance use disorders." Given that we will limit our recruitment to individuals residing in the USA only, providing SAMSHA's contact information will be appropriate. Additionally, because we will not directly interact with online participants and collect only the minimum amount of data to answer our research question, we will not know whether online participants might be pregnant or are justice-involved. However, based on the above outlined online study procedures we do not anticipate the protection of these vulnerable subjects is affected (e.g., study coercion is low if there is no interaction with the study team; materials and methods do not pose an additional risk for pregnant individuals).

Prolific (https://www.prolific.co/researchers) will be used to recruit online participants. Prolific is a panel-based platform on which individuals can create an account to participate in online research.

Prolific's privacy policy meets the standards of the European, General Data Protection Regulation law (GDPR), and personally identifiable information from participants cannot and will not be collected through Prolific. More specifically, although Prolific will collect IP addresses, it is not possible for researchers to gain access to such or any personally identifiable data. Instead, participants have a Prolific ID that we will collect to provide reimbursement for study participation at a rate of $8-$16/hour (exact rate will depend on the complexity and length of individual tasks as well as Prolific's suggested rate) for a study duration of 60-90 minutes. Reimbursement occurs after the approval of study completion submissions by the research team. Although it is possible to reject submissions within 21 days of completion and forgo reimbursement to a participant, this is only allowed for pre-specified valid reasons (and Prolific may overturn rejections in certain occasions). In case of issues with participation, Prolific IDs can be used to contact participants through Prolific's email feature to protect the personal email addresses of both researchers and participants.

To run the experimental contextual learning and memory task as well as administer the questionnaires, Prolific will link to 'Pavlovia' and Brown University's instance of Qualtrics. Pavlovia is a place to run, share, and explore experiments online and which can run the 'PsychoPy' script of our experimental task, see also https://pavlovia.org/docs/home/ethics. Like Prolific, Pavlovia is GDPR compliant their server logs, which contain IP addresses, will not be shared with and cannot be accessed by the research team and will not be linked to participant data. The PsychoPy experimental script will automatically log the completion date of the experiment. Aside from this completion date no other personal identifiers will be collected. Questionnaire responses captured through Qualtrics will be collected in a fully anonymized manner, see https://ithelp.brown.edu/kb/articles/use-qualtrics-for-human-subjects-research-anonymize-responses.

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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 filed cabinets on-site. 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 for data analysis in this protocol and future investigations.

3. **Assurances that the PHI will not be Re-used or Disclosed:**
   Information collected will only be used for purposes described below and will be treated as confidential. PHI collected as part of the study protocol will be shared only with collaborators and shared in de-identified form only. PHI gained from medical record searches will be specifically used to identify interested patient participants for the above-mentioned study. 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. PHI is only needed for activities preparatory to research☐YES ☒NO

6) DESCRIPTION OF PHI TO BE COLLECTED UNDER WAIVER

To identify potential participants, we may need to review the medical records of patients at Butler Hospital either after potential participants reached out to us because they are interested in participating or because they take part in Butler Hospital clinics (e.g. Partial Hospital Programs/Women's Partial Program). This will involve their name, admitting information, treating clinician, and diagnosis. All PHI will be kept confidential within research team and clinic staff. Potential participants who are identified from reviewing the medical records of Butler Hospital clinics (e.g. Partial Hospital Programs/Women's Partial Program) will be given an outreach handout asking if they would be interested in participating/consent to being contacted. Medical records of participants who inquire about the study may be reviewed in order to confirm inclusion/exclusion criteria, and. PHI to be obtained includes patient demographic information (age, gender), contact information (name, phone number), treatment provider, and medical and treatment history.

7) ADVERTISEMENTS

ONLINE ADVERTISEMENT TEXT:
PROJECT RISE in PTSD
Research Investigating Stimulation for Extinction in PTSD

We are looking for people who are diagnosed by a clinician with posttraumatic stress disorder and who are interested in being part of a research study in which we look at the effects of a very low level of electrical current on the scalp (called tDCS) on emotional learning and memory. This study will involve four or five study visits. On the first visit we will do a screening and we might ask you to get a brain scan on a second visit. On visits three, four and five you will do a computer task that tests emotional learning and memory. During one of those days you may or may not also receive the very low level of electrical current through two electrodes attached to your head and may or may not also get a brain scan.
You may qualify if you:

- Are between 18-70 years-old
- Speak and read English fluently
- Have no history of closed-head injury or neurological disease
- Have no implanted electronic hardware, such as metal implants, pacemakers or medication pumps or metal in the head
- Have no current or history of psychosis or bipolar depression
- Have no holes in the skull made by trauma or surgery
- Have no history of epilepsy or seizures
- Are not pregnant

Number of visits: 4 or 5
Duration of visits: Visit 1 about 3 hours, visits 2-5 about 1 hour each visit.
[Participants will earn compensation for research participation.] or [Participants can earn up to $170-$270.
If interested in learning more, please contact:

[Insert RA name]
Phone: [Insert study phone number]

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

See attached