Transcranial Direct Current Stimulation (tDCS) as a Treatment for Acute Fear

NCT02410954

Document Date: 11/06/2018

Study Application (Version 1.13)

1.0 General Information

***Enter the full title of your study:**

Transcranial Direct Current Stimulation (tDCS) as a Treatment for Acute Fear

***Enter the study number or study alias**

tDCS Treatment of Acute Fear
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

2.0 Add Department(s)

2.1 List the departments associated with this study. The Principal Investigator's department should be Primary.:

Primary Dept?	Department Name
○	**UCSF** - *133102* - M_Psych-Core-Admin
○	**UCSF** - *133100* - M_Psychiatry

3.0 List the key study personnel: (Note: external and affiliated collaborators who are not in the UCSF directory can be identified later in the Qualifications of Key Study Personnel section at the end of the form)

3.1 *Please add a Principal Investigator for the study:

Krystal, Andrew MD

Select if applicable

☐ Department Chair ☐ Resident

☐ Fellow

If the Principal Investigator is a Fellow, the name of the Faculty Advisor must be supplied below.

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Marton, Tobias F, MD/PhD
Study Clinician
Scangos, Katherine MDPhD
Study Clinician
Seritan, Andreea L, MD
Study Clinician

B) Research Support Staff

Andrews, Katherine B
Study Coordinator
Lee, Andrew
Technician

3.3 *Please add a Study Contact:

Andrews, Katherine B
Krystal, Andrew MD

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

3.4 If applicable, please add a Faculty Advisor/Mentor:

3.5 If applicable, please select the Designated Department Approval(s):

Add the name of the individual authorized to approve and sign off on this protocol from your Department (e.g. the Department Chair or Dean).

Initial Screening Questions

Updated June 2017

4.1 * PROJECT SUMMARY: (REQUIRED) Give a brief overview of this project (250 words or less). Tell us what this study is about, who is being studied, and what it aims to achieve. If you have an NIH Abstract, paste it here: Click on the orange question mark to the right for more detailed instructions.

This NIMH-funded project was started at Duke University in 2015 and is being transferred to UCSF because the PI moved from Duke to UCSF. Once the study is IRB approved and initiated at UCSF all patient-related activities at Duke will cease. Modeling of tDCS electric field distribution for new tDCS electrode placements to be tested at UCSF will continue at Duke. We have included below the abstract of our grant.

NIH ABSTRACT:

This application responds to RFA-MH-15-300 (Exploratory Clinical Trials of Novel Interventions for Mental Disorders [R21/R33]) by proposing to translate neuroscience findings into a novel non-pharmacologic treatment for Acute Fear, a Research Domain Criteria (RDoC) construct common to many DSM defined anxiety disorders. The neuroscience findings which serve as the basis for this effort are an extensive preclinical body of work documenting that the region of the brainstem known as the locus coeruleus (LC) plays a key role in mediating symptoms of Acute Fear. We capitalize on evidence that LC activity can be non-invasively measured with pupillometry and our pilot data indicating that we can modulate LC activity with transcranial direct current stimulation (tDCS) applied via electrodes attached to the skin/scalp. Our approach is to develop tDCS as a means of inhibiting LC activity and then determine if this diminishes symptoms of Acute Fear.

Our translational effort will consist of two stages, a 2 year R21 phase where we establish feasibility, tolerability, safety, and proof-of-concept (POC) in terms of capacity to engage the neural target, followed by a 3 year R33 parallel-group, double blind, controlled trial. In the R21 phase we will employ an iterative approach where we use electric field modeling with a realistic head model to identify promising treatment electrode placements which we will test across a series of electrical doses in 3 cohorts of healthy controls to attempt to identify a tDCS treatment electrode configuration with which

we can identify a dosage in each subject that is: (1) tolerable (5-point Likert ratings of no more than mild discomfort); and (2) engages the target neural circuitry by transiently inhibiting LC activity as reflected in prevention of the pupil dilation response in the anxiety task or to rare stimuli in the auditory oddball task (AOT), tasks which reliably activate LC. If successful we will proceed to a 3 year R33 parallel group trial where 60 healthy volunteers are randomized to electrical dose-personalized active tDCS vs an active control therapy (tDCS that delivers the same skin current density as the active but does not affect LC) here clinical symptoms Acute Fear, the primary outcome, are elicited by inhalation of 7.5% CO2. Future development viability will be assumed if there is preliminary evidence that engaging the target (inhibiting LC) safely diminishes clinical Acute Fear symptoms.

Our broad scientific goal is to evaluate if engagement of the target brain circuitry, inhibition of LC, is a viable target for treating Acute Fear. This is of high public health importance as Acute Fear is an extremely widespread and debilitating problem and current treatment options are quite limited.

4.2 * HUD DEVICE: (REQUIRED) Does this application involve a Humanitarian Use Device (HUD):

No
Yes, and it includes a research component
Yes, and it involves clinical care ONLY

4.3 * TYPE OF RESEARCH: (Click the Help link for definitions and guidance): (REQUIRED)

Biomedical research
Social, behavioral, educational, and/or public policy research
Hybrid - includes aspects of BOTH types of research (check this option if your research is mainly social
/behavioral but also involves specimen collection or blood draws to look at biological measures)

4.4 * SUBJECT CONTACT: (REQUIRED) Does this study involve ANY contact or interactions with participants:

Yes (including phone, email or web contact)
No (limited to medical records review, biological specimen analysis, and/or data analysis)

4.5 * RADIATION EXPOSURE: Does your protocol involve any radiation exposure to patients/subjects EITHER from standard care OR for research purposes (e.g., x-rays, CT-scans, DEXA, CT-guided biopsy, radiation therapy, or nuclear medicine including PET, MUGA or bone scans): (REQUIRED)

Yes No

4.6 * RISK LEVEL: (REQUIRED) What is your estimation of the risk level, including all screening procedures and study activities (Help Text updated 9/13):

Minimal risk
Greater than minimal risk

4.7 * REVIEW LEVEL: (REQUIRED) Requested review level (Click on the orange question mark to the right for definitions and guidance):

Full Committee
Expedited
Exempt

4.11 * CLINICAL TRIAL: (REQUIRED) Is this a clinical trial? According to The World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) a clinical trial is:

- **Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.**

ICMJE requires registration of a clinical trial in a public database (such as ClinicalTrials.gov) prior to enrollment, for eventual publication of results in member biomedical journals. Guidance: Public Law 110-85 requires that all investigators who perform an *applicable clinical trial* must ensure that the trial is registered on a government web site called ClinicalTrials.gov. The FDA requires registration for "applicable clinical trials," defined as follows:

- **For any trials of drugs and biologics: controlled clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation.**
- **For trials of biomedical devices: controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and pediatric post-market surveillance.**

For additional information on the ClinicalTrials.gov registration process at UCSF and the definition of a clinical trial for purposes of registration, visit the ClinicalTrials.gov section of the UCSF Clinical Research Resource HUB.

○ Yes ◉ No

Clinical Trial Registration

"NCT" number for this trial:

4.13 * INVESTIGATOR-INITIATED: (REQUIRED) Is this an investigator-initiated study:

◉ Yes ○ No

4.14 SCIENTIFIC REVIEW: If this study has undergone scientific or scholarly review, please indicate which entity performed the review (check all that apply):

☐ Cancer Center Protocol Review Committee (PRC) (Full approval is required prior to final CHR approval for cancer-related protocols.)
☐ CTSI Clinical Research Services (CRS) Advisory Committee
☐ CTSI Consultation Services
☐ Departmental scientific review
☑ Other:

* Specify **Other: (REQUIRED)**

NIH review

4.15 * STEM CELLS: (REQUIRED) Does this study involve human stem cells (including iPS cells and adult stem cells), gametes or embryos:

◉ No
○ Yes, and requires CHR and GESCR review
○ Yes, and requires GESCR review, but NOT CHR review

4.16 * FINANCIAL INTERESTS: (REQUIRED) Do you or any other responsible personnel (or the spouse, registered domestic partner and/or dependent children thereof) have financial interests related to this study:

○ Yes ◉ No

5.0 Funding

5.1 * FEDERAL FUNDING: (REQUIRED) Is this study currently supported in whole or in part by Federal funding, *even by a subcontract*, OR has it received ANY Federal funding in the past:

(•) Yes ( ) No

The IRB is required to compare the grant to the IRB application for studies with federal support. Indicate which portion of your grant you will be attaching:

- [x] For NIH grants, the Research Plan, including the Human Subjects Section
- [ ] For other federal proposals (contracts or grants), the section of the proposal describing human subjects work
- [ ] The section of your progress report if it provides the most current information about your human subjects work
- [ ] The grant is not attached. The study is funded by an award that does not describe specific plans for human subjects, such as career development awards (K awards), cooperative agreements, program projects, and training grants (T32 awards) OR UCSF (or the affiliate institution) is not the prime recipient of the award

5.2 * DoD INVOLVEMENT: Is this project linked in any way to the Department of Defense (DoD): (REQUIRED)

( ) Yes (•) No

5.3 SPONSORS: Identify all sponsors and provide the funding details. If funding comes from a Subcontract, please list only the Prime Sponsor:

External Sponsors:

View Details	Sponsor Name	Sponsor Type	Awardee Institution	Contract Type:	UCSF RAS "P number" or eProposal number	UCSF RAS System Award Number ("A" + 6 digits)
⊟	NIH Natl Institute of Mental Health	01			P0518217	

Sponsor Name:	NIH Natl Institute of Mental Health
Sponsor Type:	01
Sponsor Role:	Funding
CFDA Number:	
Grant/Contract Number:	
Awardee Institution:	
Is Institution the Primary Grant Holder:	No
if No, then who is the Primary Grantee?	
Contract Type:	
UCSF RAS "P number" or eProposal number:	P0518217
UCSF RAS System Award Number ("A" + 6 digits):	

Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	Transcranial Direct Current Stimulation (tDCS) as a Treatment for Acute Fear" submitted in response to the request for applications: RFAMH-15-300 (Exploratory Clinical Trials of Novel Interventions for Mental Disorders [R21/R33])
PI Name: (If PI is not the same as identified on the study.)	
Significant Discrepancy:	The grant was initially awarded to Duke, but is now being transferred to UCSF because the PI has moved from Duke to UCSF.

If the funding is coming through UCSF and you don't know the A or P number, you can search the eProposal side for the contract or grant (this does NOT replace adding the sponsor by name above AND entering the A or P number):

Project Status	Proposal Number	Project Title	Principal Investigator
Awarded	P0518217	R21 Duke University Transfer	Andrew Krystal MD
		Transcranial Direct Current Stimulation (tDCS) as a Treatment for Acute Fear	

Other Funding Sources and Unfunded Research - Gift, Program, or Internal Funding (check all that apply):

- ☐ Funded by gift (specify source below)
- ☐ Funded by UCSF or UC-wide program (specify source below)
- ☐ Specific departmental funding (specify source below)
- ☐ Unfunded (miscellaneous departmental funding)
- ☐ Unfunded student project

6.0 Sites, Programs, Resources, and External IRB Review

6.1 UCSF AND AFFILIATED SITES (check all that apply):

- ☑ UCSF (including Laurel Heights and all the other sites outside the main hospitals)
- ☐ Parnassus
- ☐ Mission Bay
- ☐ China Basin
- ☐ Mount Zion
- ☐ Helen Diller Family Comprehensive Cancer Center
- ☑ Langley Porter Psychiatric Institute
- ☐ San Francisco General Hospital (SFGH)
- ☐ SF VA Medical Center (SF VAMC)
- ☐ Blood Centers of the Pacific (BCP)
- ☐ Blood Systems Research Institute (BSRI)
- ☐ Fresno Community Medical Center
- ☐ Gallo
- ☐ Gladstone
- ☐ Jewish Home

☐ Institute on Aging (IOA)
☐ SF Dept of Public Health (DPH)

6.2 LOCATIONS: At what locations will study visits and activities occur:

Langley Porter Psychiatric Institute, Parnassus Heights campus, 401 Parnassus Ave, Rooms A312, A307D

6.3 OFF-SITE PROCEDURES: Will any study procedures or tests be conducted off-site by non-UCSF personnel:

○ Yes ◉ No

6.4 RESEARCH PROGRAMS: Check any UCSF research programs this study is associated with:

☐ Cancer Center
☐ Center for AIDS Prevention Sciences (CAPS)
☐ Global Health Sciences
☐ Immune Tolerance Network (ITN)
☐ Neurosciences Clinical Research Unit (NCRU)
☐ Osher Center
☐ Positive Health Program

6.5 * CTSI CRS SERVICES: (REQUIRED) Will this study be carried out at one of the UCSF Clinical Research Services (CRS) units or utilize CRS services:

○ Yes ◉ No

6.6 * MULTI-CENTER TRIAL: (REQUIRED) Is this a multicenter research trial? By multi-center trial, we mean a study where the protocol is developed by an industry sponsor, consortium, a disease-group, etc., who then selects sites across the nation or in different countries to participate in the trial. The local sites do not have any control over the design of the protocol.

○ Yes ◉ No

6.7 OTHER SITE TYPES: Check all the other types of sites not affiliated with UCSF with which you are cooperating or collaborating on this project: Do NOT check any boxes below if this is a multi-center clinical trial, UCSF is just one of the sites, and neither UCSF nor its affiliates are the coordinating center.

☐ Other UC Campus
☑ Other institution
☐ Other community-based site
☐ Foreign Country
☐ Sovereign Native American nation (e.g. Navajo Nation, Oglala Sioux Tribe, Havasupai, etc.)

6.10 * RELYING ON AN EXTERNAL IRB: Does this application include a request to rely on an a central IRB (other than the NCI CIRB) or an external IRB (UC, commercial, or institutional): (REQUIRED)

○ Yes ◉ No

7.0 Outside Site Information

7.1 Outside Site Information

Click "Add a new row" to enter information for a site. Click it again to add a second site again to add a third site, a fourth site, etc.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

Duke University School of Medicine

Contact name:

Steven Szabo, MD, PhD

Email:

Phone:

For Federally-funded studies only, corresponding FWA#:

*** The research at this site will be reviewed by:**

- ○ The non-affiliated site's IRB or a private IRB
- ○ The non-affiliated site is requesting UCSF to be the IRB of record for this study
- ◉ The non-affiliated site is not engaged in the human subjects research and has provided a letter of support

If the other site's IRB approval letter is available now, attach it to the application. If the IRB approval letter is not yet available, submit it once you receive it.

Or, if the other site is **not engaged** in human subjects research, attach the letter of support to your application.

8.0 Research Plan and Procedures

8.1 This new consolidated section requests information about:

- **Hypothesis**
- **Aims**
- **Study Design**
- **Background and Significance**

- **Preliminary Studies**
- **Procedures**
- **Statistical Methods**
- **References**

Later sections include:

- **Drugs and Devices**
- **Sample Size, Eligibility, and Subjects**
- **Recruitment and Consent**
- **Risks and Benefits**
- **Data and Safety Monitoring Plan**
- **Confidentiality, Privacy and Security**
- **Financial Considerations**
- **Qualifications of Personnel**
- **Other Approval and Registrations**

8.2 HYPOTHESIS: Describe the hypothesis or what the study hopes to prove (Help Text updated 9/13):

Locus coeruleus (LC) norepinephrine (NE) neuron activity has been convincingly linked to regulation of acute fear. This study will address whether pupillometry (measurement of pupil size) will reflect LC NE activity elicited by inhalation of 7.5% CO2 (an established method for activating LC and inducing acute fear) in humans and if transcranial direct current stimulation (tDCS) can block both the induced pupil effects and associated experience of fear. Our hypothesis is that tDCS has promise as a treatment for acute fear as evidenced by tDCS administration targeting the LC inhibiting both the pupil dilatory response and fear response to 7.5% CO2 inhalation. A 2 year R21 phase will establish feasibility, tolerability, safety, and proof-of-concept (POC) in terms of capacity to block the pupil response to 7.5% CO2 followed by a 3 year R33 parallel-group, double-blind, randomized, controlled trial which will assess the degree to which blocking the pupil response to CO2 inhalation with tDCS prevents the development of acute fear in response to CO2 inhalation.

8.3 AIMS: List the specific aims:

Specific Aim 1: R21**-** Establish methods required for R33 controlled trial of transcranial direct current stimulation (tDCS) treatment of Acute Fear
Specific Aim 2: R21- Establish feasibility, tolerability/safety, and Proof of Concept (POC) (determine degree to which we can engage the locus coeruleus [LC]) of tDCS as an intervention for acute fear.
Specific Aim 3: R33 – Conduct a parallel group, double-blind, randomized, controlled trial of dose-personalized tDCS (current amplitude dose chosen to prevent pupil dilation occurring with an auditory oddball task and be well tolerated) in 60 healthy subjects given CO_2 to elicit fear to assess safety and efficacy of tDCS as a treatment for Acute Fear

8.4 DESIGN: Briefly describe the study design (e.g., observational, interventional, randomized, placebocontrolled, blinded, cross-over, cross-sectional, longitudinal, pharmacokinetic, etc.):

Design & Procedures

1. Subject recruitment: Participants will be recruited in Dr. Krystal's laboratory at UCSF. We plan to enroll a total of 240 subjects healthy volunteers (age range: 21-65 years) in order to complete 100 for the entire effort (R21 and R33 Phases combined). This corresponds to enrolling 68 subjects in the R21 (34/year) and 172 (58/year) during the R33 phase. This takes into account the expected rate of failure to: have a pupillary response to the fear conditioning paradigm (25%) and CO2 challenge (50% - relevant for last 10 R21 and all R33 subjects); and to meet other screening criteria (see inclusion and exclusion criteria sections). These subjects will be recruited from the local community using posted flyers.

2. R21/R33 Components: R21 Phase:

First 30 Subjects, following the screening visit, these subjects will undergo 2-3 sessions separated by 1 week in which a promising electrode configuration (three promising configurations will each be tested in a cohort of 10 subjects) will be used with tDCS stimulation at increasing electrical dosage during which pupillometry will be carried out to determine the Anxiety Task (a test of responses to electrical pulses delivered to the fingers) or Auditory Oddball Test (AOT; a test of responses to rare vs common sounds) response. During pupillometry while undergoing tDCS, ECG, EEG, respiratory rate, or galvanic skin conductance measures may be obtained. A maximum of 5 total tDCS dosages and sham will be tested.

Last 10 Subjects. These subjects will take part in a double-blind, controlled, randomized, cross-over study over 3 sessions following their screening visit. At session 1 subjects will undergo electrical dose titration with the tDCS electrode configuration resulting from the 3 rounds of optimization using the same procedure as in the first 30 subjects to determine the lowest well-tolerated dose that suppresses the pupil dilation response to the Anxiety Task or Auditory Oddball Test, except that a maximum of 5 tDCS dosages will be tested at this session. At the second and third sessions (1 week apart) subjects will receive doseoptimized tDCS and the control treatment with order randomized along with 7.5% CO2 (to evoke an LC response) for 20 minutes. The 7.5% CO2 will be delivered pre-mixed as provided by Airgas. 7.5% CO2 is commonly and safely used in the field of study. A mixture of CO2 7.5%/O2 21%/N 71.5% with be purchased premixed from Airgas and shipped to UCSF. At these sessions, the VAS-A and STA-I will be administered 5 minutes prior to and just after the 20 minute session and VAS-A will also be obtained at 5, 10, 15, and 20 minute points of the CO2 inhalation. tDCS will be administered during the last 5 minutes of the 20 minute CO2 inhalation period. Subjects will be monitored for an hour post-session for safety and will undergo study physician assessment to determine suitability to leave. Following the 2nd treatment session participation will end except that subjects will be called the next day to assess for adverse effects and appropriate care will be given if any are found.

R33 Phase: 60 subjects will participate in a double-blind, randomized, controlled, parallel-group trial. They will be randomized to either active or control treatment and at the first post-screening visit they will undergo electrical dose titration as described above for the treatment they are randomized to. For all titrations, during the 5 minutes between tDCS treatments an unblinded member of the study team not having contact with the subjects will compute their Anxiety Task or Auditory Oddball Test response (these tests will be used to determine optimal dosing in terms of the tDCS level that blocks the pupil response in these tests) and convey to the tDCS treatment physician whether to continue or stop titration. Subjects randomized to the control treatment will undergo a sham titration where the stop level will be randomly selected from the distribution of titration outcomes occurring in the R21 phase. Subjects will then return in 1 week and undergo optimal dose tDCS or control treatment for a single treatment session as described in the prior paragraph. Primary outcome will be the VAS-A "fearful" rating obtained at the end of tDCS/CO2 inhalation. Anxiety Task or AOT pupil responses will be obtained every 10 minutes after the end of the tDCS/CO2 inhalation period to map the duration of persistent effects on LC (heart rate and skin conductivity will also be obtained as exploratory measures). At the end of this session participation will end except that subjects will be called the next day to assess for adverse effects and care given if necessary. Data from the R21 phase will be used to provide justification for the larger R33 study, and prior to initiation of the R33 phase, the study will be submitted to the IRB for review/approval.

8.5 BACKGROUND AND SIGNIFICANCE: Briefly provide the background and significance of this study (e.g. why is this study needed) (space limit: one half page):

If this is a first in humans study, please summarize the safety data from the animal studies. For pediatric drug or device studies, please identify if this is the first study in pediatric populations.

The National Institutes of Mental Health (NIMH) has recently identified that a major limitation to the understanding of neuropsychiatric disorders and the development of treatments for these conditions has been the inability to identify key dimensions of observable behavior that are central to these disorders and linked to underlying neurobiology by measurable biomarkers. This proposal is intended to address this problem by establishing that

measurement of pupil size using pupillometry, which has been established to reflect the activity in norepinephrine neurons in the locus coeruleus, is a biomarker of the acute fear dimension of observable behavior and that the acute fear response can be blocked with transcranial magnetic stimulation (tDCS) targeted to inhibit locus coeruleus neurons. This is intended to establish that tDCS is promising for serving as a much needed treatment for acute fear which is a core feature of neuropsychiatric conditions such as anxiety disorders for which improved treatments are needed.

We will first establish feasibility and proof of concept by employing the Anxiety Task or Auditory Oddball Test which activate the Locus Coeruleus (LC) and assessing whether we can block the activation of LC neurons as measured with pupillometry via administering tDCS targeted to inhibit LC neuronal activity. We will then further establish proof of concept by using pupillometry to assess whether we are able to inhibit the locus coeruleus neuronal response the adminsitration of 7.5% CO_2, an established means of activating locus coeruleus neurons and provoking fear responses, with tDCS targeted to inhibit locus coeruleus activity as measured by pupillometry. If these proof of concept tests are successful, we will then proceed to carrry out a clinical trial in healthy controls where we will test whether tDCS targeted to inhibiting locus coeruleus neurons blocks the clinical acute fear response to 7.5% CO2 administration.

8.6 PRELIMINARY STUDIES: Briefly summarize any preliminary studies relevant to your proposed research (space limit: one half page):

Preclinical Work on Brainstem Circuitry Modulating LC Function. Among the bases for this proposal is preclinical work carried out by Co-Investigator Dr. Szabo on the brainstem circuits which modulate locus coeruleus (LC) activity. This work supports the proposed effort because it suggested that we could target a brainstem circuit with a treatment such as tDCS and modulate LC activity without having to target the LC itself which is quite small. His work in rats documented that 21-day but not acute or 2-day SSRI therapy attenuates LC spontaneous firing activity paralleling the lag in onset of therapeutic action of antidepressant drugs in anxiety disorders. A brainstem LC modulatory circuitry was found that explains why time is needed to decrease LC activity. Further, he found that manipulations such as paw pinch transition LC NE neurons from a tonic pacemaker to a burst firing pattern, and that anxiogenic drugs also enhance tonic firing rates and bursts in LC activity (Szabo et al., 2004). Dr.Szabo's work supports that interventions which augment and reduce LC activity can induce and attenuate fear and anxiety, respectively.

Vestibular Stimulation with Direct Alternating Current (tACS). Dr. Krystal completed a doubleblind, sham-controlled study of tACS vestibular stimulation in healthy volunteers as a treatment for insomnia. This study also speaks to Dr. Krystal's experience in successfully leading double-blind, controlled, transcranial electrical stimulation studies where stimulation is carried out targeting a region adjacent to the brain stem.

Electric Field Modeling Using a Realistic Head Model. Co-investigators Peterchev and Deng have extensive experience creating models of the electric field induced in the brain by various transcranial electric stimulation paradigms such as tDCS. These models include realistic rendering of the head anatomy based on an MRI scan, and allow the determination of the electric field strength in specific brain structures such as the LC. This work speaks to our capacity to carry out the proposed electric field modeling and optimization of tDCS electrode configuration.

Study Demonstrating Link of Clinical Fear Symptoms and Resting Pupil Diameter. The team of investigators carried out a pilot study identifying mean resting pupil diameter as a biomarker of selfreported clinical symptoms of fear/anxiety which supports the use of this measure in the proposed study and the team's ability to successfully obtain that measure. They recruited 19 subjects (11

medication-free patients with mood and anxiety spectrum disorders and 8 healthy controls. A validated anxiety scale with well-established psychometric properties was employed: the Hamilton Anxiety Rating Scale (HAM-A). We found that greater pupil diameter was associated with greater HAM-A ($r=0.56$; $p< 0.02$) and PAS ($r=0.53$; $p< 0.02$) scores (See Figure 2). Although these measures do not directly reflect Acute Fear, it can be assumed that those with significantly elevated levels of fear in the prior week are more likely to experience fear in the laboratory. However, this analysis underestimates the strength of the relationship of mean resting pupil diameter and acute fear that will be seen in the proposed study where all subjects will be induced to have fear during testing in the laboratory and we will attempt to mitigate the fear and LC activation with tDCS. Based on these findings we propose to employ mean resting pupil diameter as a biomarker of target engagement (LC activation level) occurring in association with the induction of Acute Fear symptoms induced by 7.5% CO2 in the proposed R21 and R33 studies.

Pilot study of administering tDCS to modulate LC activity in healthy controls. The team of investigators carried out a pilot study in which we tested 2 two-electrode tDCS electrode configurations that had potential to affect the region of the LC based on the rough general principal that the LC should lie between the two treatment electrodes. We employed measurement of pupil diameter in the auditory oddball test (AOT) to determine our capacity to modulate LC activity in terms of whether we could affect the degree of separation between the pupil diameter response to rare vs common tones. It was understood that with this gross electrode configuration approach we were as likely to enhance as inhibit LC activity, though we assumed that doing either was proof-of-concept that we could modulate LC activity with tDCS. We administered the highest well tolerated tDCS stimulus electrical dosage for each subject which varied from 2–4 mA for the 5 people studied.
It is important to note that the 4 mA maximum dosage is within recommended safety limits. We evaluated tDCS with: 1) the electrodes placed over the ears (external auditory meatus) and; 2) one electrode at the inion (notch on the back of the head at the top of the neck) and the other just under the chin. Pupillometry was carried out during the auditory oddball tasks (AOT) where two tones are played one more frequently than the other and the rare tones are well-established to lead to a neural response approximately 300 msec after the rare tones are played. We found that treatment was well-tolerated in general. We were able to find at least one electrode configuration and polarity (orientation of anode and cathode) associated with a tolerable stimulus intensity for all subjects that had a statistically significant effect on the pupillary AOT response. In 4/5 subjects there was an electrode configuration where the LC pupil dilation response to the rare stimuli was significantly suppressed by tDCS compared with both immediate pre and immediate post-stimulation testing (see Figure 3 for example). In 1 subject the response to the rare tones was enhanced by stimulation. In two of the subjects the direction of effect (suppression or enhancement) differed for the electrode configurations and polarities tested. These findings suggest that we can modulate LC function with tDCS with a substantial effect size, though the findings further indicate that electric field modeling will be needed to determine optimal treatment electrode placement given that effects appear to vary from person-to-person and that it is not possible to predict effects in a simple way, such that without modeling and iteration, we may be as likely to augment as inhibit LC activity, at least in some individuals. The findings also indicate that the effect size of inhibition is large enough to be statistically significant at the $p< 0.05$ level in a single trial in an individual. These findings serve as a key basis for the proposed effort, support the need for work to determine optimal electrode placement before trials of tDCS for acute fear could be carried out, and support the use of the AOT as a target engagement measure.

8.7 * TREATMENT PROTOCOL: Is this a treatment study, i.e. does this study intend to provide treatment to individuals with a medical or psychological condition: (REQUIRED)

○ Yes ◉ No

8.8 * COMMON RESEARCH ACTIVITIES: Types of research activities that will be carried out. Check all that apply and describe in more detail in the 'Procedures / Methods' section: (REQUIRED)

- ☑
- ☑ Interviews, questionnaires, surveys
- ☐ Educational or cognitive tests
- ☐ Focus groups
- ☑ Observation
- ☐ Non-invasive imaging or testing (MRI, EEG, pulse oximetry, etc.)
- ☐ Administration of contrast agent
- ☐ Imaging procedures or treatment procedures that involve radiation (x-rays, CT scans, CT-guided biopsies, DEXA scans, MUGA or PET scan)
- ☑ Biopsy conducted solely for research purposes
- ☐
- ☐

Use of placebo
Sham surgical procedure
Collection of data from wearable tech such as Fitbit, Apple Watch, Garmin, motion actigraphs, etc.)
Fitness tests or other exertion activities
Use of mobile health apps or other apps
Social media-based research activities
None of the above

8.9 * PROCEDURES / METHODS: (REQUIRED)

For clinical research, list all study procedures, tests and treatments required for this study, including when and how often they will be performed. If there are no clinical procedures, describe the research activities.

If some of the activities would occur even if the person were not in the study, as in the case of treatment or tests performed for diagnostic purposes, clearly differentiate between those activities that will be done solely for research purposes and those that are happening as part of routine care.

Examples may include:

- additional scans outside standard clinical diagnosis or monitoring
- additional biopsies to collect tissue for research extra clinic visits
- extra lab tests not required for clinical care

If you have a procedure table, attach it to the submission with your other study documents.

1. **Pupillometry Procedure:** We will employ a Tobii Pro eye tracking system to measure pupil response. Pupil diameter will be recorded continuously from the each eye at a sampling rate of 60 Hz via a sensor bar attached to a computer monitor. We will capture pupil size at baseline, in response to the Anxiety Task or Auditory Oddball Test (AOT), pain-induced conditioned fear test, and administration of 7.5% CO2. Data will be segmented into epochs from 0 to 12 s relative to the acquisition onset of each stimuli or experimental condition. An average pupil diameter measure will then be calculated for the corresponding volume by taking the mean across the remaining non-artifactual samples in that epoch. During tDCS the pupil diameter will be averaged over 1 minute periods while subjects are staring at a dark screen in a dark room. For 7.5% CO2 response the pupil diameter will be averaged over 1 minute periods while subjects are staring at a dark screen in a dark room. This will be computed at baseline, and at 5, 10, 15, and 20 minutes after the start of CO2 inhalation and 5 minutes and 30 minutes post-inhalation. During pupillometry while undergoing tDCS, ECG, EEG, respiratory rate, or galvanic skin conductance measures may be obtained.

2. **Transcranial Direct Current Stimulation (tDCS):** tDCS involves non-invasive transcranial electrical stimulation using direct current with a sustained intensity of a few milliamperes and duration of up to tens of minutes. Administered in this way tDCS is a safe procedure (See Bickson et al., 2016 attached). Evidence from relevant animal models indicates that brain injury by such Direct Current Stimulation occurs at predicted brain current densities (6.3–13 A/m) that are over an order of magnitude above those produced by tDCS such as we will administer it (Bickson et al., 2016). To date, the use of conventional tDCS protocols in human trials (40 min, 4 milliamperes, 7.2 Coulombs) has not produced any reports of a Serious Adverse Effect or irreversible injury across over 33, 200 sessions and 1000 subjects with repeated sessions and including a wide variety of subjects, including persons from potentially vulnerable populations (Bickson et al., 2016). tDCS will be administered with a multichannel direct current stimulation device (NeuroConn DC stimulator MC-4, neuroCare). This device can be programmed so that the operator doesn't know the combination of electrodes being used for stimulation, and, thereby allow double-blinding. The active tDCS electrode configuration to be used will be determined with the 3 round iterative procedure described above; based on electric field modeling and personalized electrical dose titration to find the lowest dose that is well-tolerated and engages the

target in terms of inhibiting the Anxiety Task or AOT pupillary response and pain-induced conditioned fear response. Electrical dosage will be personalized for each subject by titrating dosage (gradually increasing) until the dosage is found that is both well-tolerated (no more than mild discomfort on a 5-point Likert scale) and suppresses the pain-induced conditioned fear response. If the 5-point Likert tolerability rating is greater than "mild discomfort" or if maximum amperage is reached without effect on the conditioned fear response then subject participation will terminate.

3. **Anxiety Task:** Using the eye-tracking system to track pupil changes, the subject may undergo the anxiety task which involves two different epochs: high tone and low tone. Before the anxiety task begins, the level of "annoying buzz" will be determined for the subject by the research team, based on the verbal responses from the subject. First, a low level "buzz" (set at 5V) will be presented through stimulation generated to the index and middle fingers of the subject, using the BIOPAC STM-200 Stimulator (duration of less than 0.5 seconds) by the researchers. The subject will be asked to report on a scale of 0 (not at all annoying) to 10 (extremely annoying), how the stimulus feels. The presentation of the "buzz" will increase in increments of 5-10V (with a maximum of 100V) until the subject reports a level 7 for highly annoying. The purpose of this "annoying buzz" is to be highly annoying, but not to provoke pain. Once this level is set, the anxiety task is initiated during which the subject will be seated in a dark room and instructed to focus on crosshairs displayed on a computer monitor. The anxiety task consists of two block types: (1) high tone and (2) low tone. Two tones of different frequencies (high and low) are played for 5 seconds at a time throughout a trial. Each trial lasts 12 minutes and consists of each tone (high and low) played 20 times (totaling to 40 tones at 5 seconds each). Stimulation will be delivered 50% of the time in association with either the high or low tone in a given trial (subject receives stimulation 10 times per trial). At each study visit (up to 3 visits, scheduled one week apart) for subjects 1-30, the subject will complete 4-6 trials during which tDCS will be administered at gradually increasing electrical doses during 50% of the trials. The other 50% of the trials will be administered without tDCS or with sham tDCS to establish the subject's baseline pupil response to the anxiety task. Subjects will be given a 5 minute break between each trial.

4. **Visual Analogue Scale for Anxiety (VAS-A)**. The VAS-A is the primary measure of clinical symptoms of Acute Fear in both the R21 and R33. It has been used extensively as an indicator of acute fear symptoms. It is included because it provides a reliable indicator of rapid changes of affective state. VAS-A consists of 11 items for 11 different symptoms (anxious, alert, fearful, relaxed, happy, feel like leaving, paralyzed, tense, nervous, irritable and worried) where for each item a mark is made on a 100 mm line scaled from 0 (not at all) to 100 (the most ever) to indicate symptom severity. Some of the 11 items from the VAS-A may be used during the anxiety task before, during, or after to measure changes in levels of subject anxiety from baseline to post-task administration.

5. **Generalized Anxiety Disorder-7 (GAD-7)**. The 7 item questionnaire may be administered at screening visits to identify anxiety state and trait correlations with pupil physiology.

6. **Beck Anxiety Inventory (BAI)**. This questionnaire may be administered at screening visits to identift anxiety state and trait correlations with pupil physiology.

7. **Auditory Oddball Test (AOT)**: Pupil changes may also be monitored using the eye tracking system to two pitches of tones. Some will be high pitched tones and some will be lower pitched tones. One of these will occur less frequently than the other. Multiple studies have confirmed that there is a neural response from the LC to the less common tones occurring approximately 300 msec after the less common tones accompanied by a pupil dilation response.

8. **Administration of 7.5% CO2**: Inhalation of 7.5% CO2 for 20 min will be carried out and is being employed because it elicits a well-documented fear response in healthy controls with good test-retest reliability/safety and there is evidence that it works via activation of LC. Also, repeated inhalations do not increase the risks of experiencing anxiety or having panic attacks. Subjects will be instructed to avoid alcohol for 36 h and caffeine for 12 h prior to testing and to eat a light lunch at least one hour prior to testing. A urine pregnancy test will be administered to women of childbearing potential on both days of gas exposure with a negative result needed in order to continue in study participation. Gas will be delivered via a nasal–oral face mask (Hans Rudolph, Kansas) connected via tubing to a 100 L reservoir bag filled with 7.5% CO2/21% O2/71.5% N2. Subjects will receive air through the mask in the 10 min prior to CO2 administration during which baseline measures will be obtained. In order to minimize risks of CO2 during each 20-min inhalation period, ECG monitoring and recording will occur continuously using a 12-lead ECG (Mortara Instruments) and breathing will be carefully monitored and recorded using pneumotachograph /integrator and data acquisition systems (Hans Rudolph). Breath-by-breath changes in %CO2 will be monitored continuously and recorded using a CO2 sensor connected to a data acquisition system (Hans Rudolph, SmartLab unit). EEG or galvanic skin conductance measures may also be obtained. Two members of the study team including 1 study physician will remain with the participant during inhalations as a safety measure. During gas administration and for 1 hour afterwards, subjects will undergo continuous monitoring of vital signs.

Participants will be able to terminate the inhalations at any point and will remain in the testing room until a study physician clears the subject to leave.

9. **Galvanic Skin Conductance**: Skin conductance responses can change during various levels of arousal monitored using a technique called galvanic skin conductance. Conductance values are obtained by placing two sticky patches, which are electrodes, on the palms and passing a tiny electrical charge between the two electrodes which is painless. Conductance may be measured during the anxiety task or CO2 administration.

10. **Electrocardiogram (ECG/EKG)**: Heart rate can change during various levels of arousal as measured by a 12-lead ECG system (Mortara Instruments). ECG may be measured during the anxiety task or CO2 administration.

11. **Electric Field Modeling**: Electric field simulation will include segmenting the structural MRI scan from a single subject into white matter, cortical matter, cerebrospinal fluid, skull, scalp, eyes, fat, muscle and air using Simpleware ScanIP. The volumes defining head tissues and the attached electrodes will be meshed into finite elements using the Simpleware module. The electric field will be computed using COMSOL simulation software. The electric field will be calculated in the LC and other brain regions thought to be relevant to our tDCS effort including prefrontal cortex, limbic system structures, and brain stem, which will be segmented using Brain Parser, and manually checked per published guidelines. For multielectrode targeting optimization we will first construct a head model with a multi-electrode grid. We solve for the component field solutions by sequentially activating individual electrodes relative to a reference. We then define a desired field distribution, which takes relatively large values near the target (LC), and zero value everywhere else in the brain.

8.11 INSTRUMENTS: List all questionnaires, surveys, interview, or focus group guides that will be used for this study:

1. **Mini-International Neuropsychiatric Interview (MINI)**. The MINI is a short structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders. It will be used to screen potential subjects for neuropsychiatric disorders and has acceptable reliability and reliability when used for this purpose.
2. **Treatment Tolerability Ratings**. In order to determine the tolerability of particular tDCS electrode placement and electrical stimulus intensities, subjects will rate their discomfort immediately after each tDCS stimulus on a 5-point Likert scale that has been widely used to assess the tolerability of procedures including colonoscopy, nasogastric tube insertion, burn dressing application, and orthodontic procedures. The anchors are: 0="No Discomfort", 1="Minimal Discomfort", 2="Mild Discomfort", 3="Moderate Discomfort", and 4="Severe Discomfort". We employ a cutoff of no more 2 as an indicator of acceptable tolerability.
3. **Visual Analogue Scale for Anxiety (VAS-A)**. The VAS-A is the primary measure of clinical symptoms of Acute Fear in both the R21 and R33. It has been used extensively as an indicator of acute fear symptoms. It is included because it provides a reliable indicator of rapid changes of affective state and is sensitive to the fear-inducing effects of 7.5% CO2 in healthy volunteers. VASA consists of 11 items for 11 different symptoms (anxious, alert, fearful, relaxed, happy, feel like leaving, paralyzed, tense, nervous, irritable and worried) where for each item a mark is made on a 100 mm line scaled from 0 (not at all) to 100 (the most ever) to indicate symptom severity. The "Fearful" item will be used as the single primary endpoint due to its being consistently significantly increased in prior studies of CO2 administration to healthy controls and evidence that anxiolytics can prevent 7.5% CO2 mediated increases in this measure. The other 10 VAS-A items will be secondary outcomes. For each CO2 administration ratings will be carried out at baseline (5 min prior to inhalation), and at 5, 10, 15, and 20 minutes into the inhalation and 15 minutes after inhalation ends. The peak effect will be obtained immediately after the end of the inhalation when the subjects will be asked to retrospectively rate the greatest intensity of effects experienced. A 26% increase in peak effect over baseline on the "fearful" item will be utilized as criteria for responding to CO2 challenge as recommended based on prior work which suggests that approximately 50% of subjects will meet this criterion. The VAS-A "fearful" rating at 20 minutes from the start of CO2 administration will serve as the primary outcome measure with the rating of peak effect being a key secondary outcome. The VAS-A may also be used during the anxiety task before, during, or after to measure changes in levels of subject anxiety from baseline to post-task administration.
4. **State Trait Anxiety Inventory (STAI)**. The 20 item STAI will be included as a secondary clinical symptoms measure of state anxiety occurring with CO2 administration. This was included because it has well-established psychometric properties and reflects changes in anxiety level with CO2 administration in healthy controls and anxiolytic medication attenuated the CO2 response with this measure. It consists of 20 items listing feelings and subjects rate their

current state with respect to those feelings from 1 (not at all) to 4 (very much so). It will be administered just before and just after CO2 administration.

5. **Generalized Anxiety Disorder-7 (GAD-7)**. The 7 item questionnaire may be administered at screening visits to identify anxiety state and trait correlations with pupil physiology.
6. **Beck Anxiety Inventory (BAI)**. This questionnaire may be administered at screening visits to identift anxiety state and trait correlations with pupil physiology.
7. **Adverse Effects (AE) Assessment**. The Systematic Assessment for Treatment Emergent Events (SAFTEE) will be used to monitor AEs. It is reliable and valid and used by Dr. Krystal in prior studies.

Attach any unpublished instruments in the 'Other Study Documents' section of the Initial Review Submission Packet form after completing the study application. Published instruments should NOT be attached.

8.12 * BIOSPECIMEN COLLECTION: Are you drawing any blood or collecting other biosamples (e.g. tissue, buccal swabs, urine, saliva, hair, etc.): (REQUIRED)

Yes No

○ ◉

8.25 STATISTICAL METHODS: Briefly summarize the methods and types of analyses that will be performed:

All dependent measures will be tested for distribution normality and meeting homogeneity of variance requirements for parametric statistics. Data transformations will be conducted where indicated.
1. Primary Hypotheses.

R21. Testing R21 hypotheses equates to testing if the "Go-No-Go" criteria for proceeding to the R33 are met.
1) Hypothesis 2a: We can identify an electrode configuration for active tDCS that is well-tolerated (5point Likert scale rating mild discomfort) and significantly suppress the Anxiety Task or Auditory Oddball
Task (AOT) pupil dilation response in 8/10 subjects in the 3rd round of treatment optimization. The Anxiety Task or AOT response will be determined using a repeated measures analysis of variance * (RMANOVA) with condition (common vs rare) as the independent measure and pupil diameter as the dependent repeated measure. If there is a statistically significant difference between the two conditions during treatment it will be assumed that suppression did not occur.
2) Hypothesis 1b: In 10 controls in a cross-over study, 7.5% CO2 inhalation significantly increases the VAS-A "fearful" rating compared to baseline rating. This will be tested with a RMANOVA where condition (7.5% CO2 vs air) is the independent variable and VAS-A "fearful" rating is the repeated dependent measure.
3) Hypothesis 2a, 1b, 1a: In a cross-over study, active dose-personalized tDCS significantly suppresses the LC pupil response to 7.5% CO2. This will be tested by carrying out a RMANOVA where treatment (active tDCS vs control) is the independent variable and mean resting pupil diameter is the repeated dependent measure. This will also establish that 7.5% CO2 elicits an LC response as measured by mean pupil diameter (Hypothesis 1b) and whether subjects can guess whether they received active tDCS or the control to assess the viability of the control treatment (Hypothesis 1a).
4) Hypothesis 2b: Active tDCS will be safe in terms of there being no adverse effects of more than mild severity and rated to be possibly, probably, or definitely related to treatment.

R33 Testing R33 hypotheses assesses if the criteria for proceeding to further development are met.
1) Hypothesis 3a: Dose-personalized tDCS decreases VAS-A "fearful" rating compared to sham in a parallel-group, randomized, double-blind study. This will be determined by computing the effect size in terms of Cohen's D for the tDCS vs control treatment effect on the VAS-A "fearful" rating at the expected peak CO2 effect (20 minutes after start of CO2).
2) Hypothesis 3b: tDCS is safe as indicated by the absence of adverse effects of more than mild severity rated to be possibly, probably, or definitely related to treatment.

Secondary/Exploratory Analyses. Examples of Exploratory/Secondary analyses of interest include: 1) Testing if there are significant differences between active tDCS and the control therapy on the pupillary response to CO2 in the R33 study; 2) Evaluating tDCS vs control treatment effect sizes for

other VAS-A items and the STAI in the R33 study; 3) mapping the time-course of effects on LC post-tDCS

8.26 REFERENCES: List only the 5-10 most relevant references (a separate bibliography can be attached for reference purposes if this study involves novel approaches, agents, or an emerging technology that the IRB may not be familiar with):

Bailey JE, Argyropoulos SV, Kendrick AH, Nutt DJ. Behavioral and cardiovascular effects of 7.5% CO2 in human volunteers. Depress Anxiety. 2005;21(1):18-25. PMID: 15782425

Bikson M, Grossman P, Thomas C et al., Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016. Brain Stimul. 2016 [Epub ahead of print].

Bailey JE, Kendrick A, Diaper A, Potokar JP, Nutt DJ. A validation of the 7.5% CO2 model of GAD using paroxetine and lorazepam in healthy volunteers. J Psychopharmacol. 2007 Jan;21 (1):42-9.

Koss M. Pupillary dilation as an index of central nervous system_2-adrenoceptor activiation. J Pharmacol Methods 1986;15:1–19.

Lepine J. The epidemiology of anxiety disorders: prevalence and societal costs. The Journal of Clinical Psychiatry 2002;63 Suppl 14: 4–8.

Murphy PR, O'Connell RG, O'Sullivan M, Robertson IH, Balsters JH. Pupil activity covaries with BOLD activity in human locus coeruleus. Hum Brain Mapp. 2014 Feb 7.

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., et al. Transcranial direct current stimulation: State of the art 2008. Brain Stimul (2008) 1(3):206-23.

Poma SZ, Milleri S, Squassante L, Nucci G, Bani M, Perin GI, Merlo-Pich E. Characterization of a 7% carbon dioxide (CO2) inhalation paradigm to evoke anxiety symptoms in healthy subjects. J Psychopharmacol. 2005 Sep;19(5):494-503. PMID: 16166187

Prenoveau JM, Forsyth JP, Kelly MM, Barrios V. Repeated exposure to 20% CO2 challenge and risk for developing panic attacks: a controlled 6 and 12 month follow-up in a non-clinical sample. J Anxiety Disord. 2006;20:1158-67.

Redmond DE Jr, Huang YH. Current concepts. II. New evidence for a locus coeruleusnorepinephrine connection with anxiety. Life Sci. 1979 Dec 24;25(26):2149-62. PMID: 120478

Schmitz, A., Grillon, C. Assessing Fear and Anxiety in Humans Using the Threat of Predictable and Unpredictable Aversive Events (the NPU-threat test). Nature Protocols. 2012 Feb 23;7(3):52732.

Shannon RV. A model of safe levels for electrical stimulation. IEEE Trans Biomed Eng. 1992;39 (4);424-6.

Verburg K, Pols H, de Leeuw M, Griez E (1998) Reliability of the 35% carbon dioxide panic provocation challenge. Psych Res 78: 207-214

9.1 * DRUGS AND/OR BIOLOGICS: Are you STUDYING any drugs and/or biologics that are either approved or unapproved: (REQUIRED)

○ Yes ◉ No

Note: This question is frequently answered incorrectly. If any drugs or biologics, approved or unapproved, are being administered under this protocol, you should check 'Yes' unless you are *absolutely* sure that NONE of the drugs are part of the research protocol. Tip: Ask the PI or the sponsor if you are not sure how to answer this question.

9.3 * MEDICAL DEVICES: Are you STUDYING any medical devices, in vitro diagnostics, or assays that are either approved or unapproved:(REQUIRED)

◉ Yes ○ No

9.4 * NSR: Are you requesting a Non-Significant Risk (NSR) determination for an investigational device:
(REQUIRED) Note: an NSR determination is different from an Investigational Device Exemption
(IDE). Check the Help link for more guidance on what types of devices can qualify for an NSR determination.

◉ Yes ○ No

* Explain why the use of the device in this study poses a non-significant risk:
(REQUIRED)

Transcranial Direct Current Stimulation (tDCS) TDCS involves non-invasive transcranial electrical stimulation using direct current with a sustained intensity of a few milliamperes and duration of up to tens of minutes. Administered in this way tDCS is a safe procecdure (See Bickson et al., 2016 attached). Evidence from relevant animal models indicates that brain injury by such Direct Current Stimulation occurs at predicted brain current densities (6.3–13 A/m) that are over an order of magnitude above those produced by tDCS such as we will administer it (Bickson et al., 2016). To date, the use of conventional tDCS protocols in human trials (≤40 min, ≤4 milliamperes, ≤7.2 Coulombs) has not produced any reports of a Serious Adverse Effect or irreversible injury across over 33,200 sessions and 1000 subjects with repeated sessions and including a wide variety of subjects, including persons from potentially vulnerable populations (Bickson et al., 2016). The US Food and Drug Administration (FDA) considers trials of tDCS as nonsignificantrisk, which means tDCS is without reasonable expectation of any Serious Adverse Effect (as de ned here) (Bickson et al., 2016). As of the publishing of the Bickson et al., article, the FDA "MedWatch" database search returns no reports for "tDCS" or "transcranial Direct Current Stimulation."

Attach any documentation you have from the manufacturer and/or FDA to support this determination.

9.5 LIST THE DEVICES: List the medical devices or in vitro diagnostics to be studied or used. In the device details screen you will be asked questions such as:

- **Whether the device is FDA approved or investigational**
- **Medicare device category**
- **If the device will be provided at no cost**
- **If an IDE is necessary, the IDE number, and who holds the IDE**
- **Risk category of the device**
- **FDA status of the device**

Please see the UCSF IRB website for more details about the use of devices in research, including the Investigator Checklist for Significant Risk, Non-Significant Risk, and/or IDE Exempt Device Studies Verification of IDE numbers: If the sponsor's protocol does not list the IDE number, you

must submit documentation from the sponsor or FDA identifying the IDE number for this study. Attach this documentation in the Other Study Documents section of the Initial Review Submission Packet. **If you have any correspondence from the FDA or sponsor regarding this device, please attach it to the application.**

NeuroConn DC Stimulator MC-	No Yes 4
Manufacturer/Supplier of Device	Rogue Resolutions
Medicare Category	A B
Where will the Devices Be Stored	Langley Porter Psychiatric Institute
Will Devices be supplied at no Cost	Yes
Is this a HUD (HDE)	No
HDE Number	
Is the Device FDA Approved	No
Is this a new device or a new use of an already approved device	Yes
Is an IDE necessary	No
IDE Number	
Who holds the IDE	N/A
IDE Details	
In the opinion of the sponsor, select the level of risk associated with this device	No Significant Risk

9.6 * Is this an expanded access or compassionate use protocol, meaning the primary purpose is to diagnose, monitor or treat a patient's condition, rather than the collection of safety and efficacy data of the experimental agent: (REQUIRED)

Yes No

10.1 ENROLLMENT TARGET: How many people will you enroll:

If there are multiple participant groups, indicate how many people will be in each group:

Participants will be recruited in Dr. Krystal's laboratory at UCSF. We plan to enroll a total of 240 subjects healthy volunteers (age range: 21-65 years) in order to complete 100 for the entire effort (R21 and R33 Phases combined). This corresponds to enrolling 68 subjects in the R21 (34/year) and 172 (58/year) during the R33 phase. This takes into account the expected rate of failure to: have a pupillary response to the Auditory Oddball Test (25%) and CO_2 challenge

(50% - relevant for last 10 R21 and all R33 subjects); and to meet other screening criteria (see inclusion and exclusion criteria sections). These subjects will be recruited from the local community using posted flyers.

10.3 SAMPLE SIZE JUSTIFICATION: Explain how and why the number of people was chosen. For multi-site studies, this is referring to the number that will be enrolled across all sites:

Given the nature of the R21/R33, we have few analyses for which consideration of power is relevant. These include the determination of whether there is a statistically significant difference in pupil response to the Anxiety Task or the rare and common stimuli in Auditory Oddball Task (AOT) and determination of whether in the R21 cross-over study active tDCS has a significantly greater effect on the pupil response to CO2 than sham. For the Auditory Oddball Task (AOT), in our pilot work where we were able to demonstrate differences between rare and common stimuli and the suppressing effects of tDCS (See Preliminary Studies). N=10 subjects in our R21 pilot cross-over study will be sufficient based on our pilot work (C.3.5). We estimate that the size of the effect of a dose-personalized, electrode configuration optimized tDCS vs control therapy will be at least as large as the effect size we observed in our preliminary work with a pilot electrode configuration where we found that in 4/5 subjects we could demonstrate a statistically significant suppression of the AOT pupil response compared with no stimulation which serves as a pilot proxy for the control therapy.

10.4 * PARTICIPANT AGE RANGE: Eligible age ranges: (REQUIRED)

- [ ] 0-6 years
- [ ] 7-12 years
- [ ] 13-17 years
- [x] 18-64 years
- [ ] 65+

10.5 * STUDY POPULATIONS: Data will be collected from or about the following types of people (check all that apply): (REQUIRED)

- [ ] Inpatients
- [ ] Outpatients
- [ ] Family members or caregivers
- [ ] Providers
- [ ] People who have a condition but who are not being seen as patients
- [x] Healthy volunteers
- [ ] Students
- [ ] Staff of UCSF or affiliated institutions
- [ ] None of the above

10.6 * SPECIAL SUBJECT GROUPS: Check the populations that may be enrolled: (REQUIRED)

- [ ] Children / Minors
- [ ] Subjects unable to consent for themselves
- [ ] Subjects unable to consent for themselves (emergency setting)
- [ ] Subjects with diminished capacity to consent
- [ ] Subjects unable to read, speak or understand English
- [ ] Pregnant women
- [ ] Fetuses
- [ ] Neonates
- [ ] Prisoners
- [ ] Economically or educationally disadvantaged persons
- [x] None of the above

10.7 INCLUSION CRITERIA: Briefly describe the population(s) that will be involved in this study. Include anyone that data will be collected from or about (e.g. patients, healthy controls, caregivers, providers, administrators, students, parents, family members, etc.):

Inclusion/Exclusion criteria were chosen to allow us to meet study aims and are comparable to those used in Dr. Krystal's prior study of transcranial alternating current (tACS) vestibular stimulation of healthy controls. Inclusion Criteria. 1) Age between 21-65; 2) Use of effective method of birth control for women of childbearing capacity; 3) Willing and able to provide informed consent; 4) Have a significant difference between the mean pupil diameter in response to rare vs common tones in the Auditory Oddball Test (AOT) or the Anxiety Task; 5) The 10 subjects in the R21 cross-over study and all of the R33 subjects must have a 26% increase in VAS-A "fearful" response to 7.5% CO_2 at the first CO_2 challenge session; 6) Able to follow study procedures.

10.8 EXCLUSION CRITERIA: List any exclusion criteria (e.g. reasons why someone would not be included in the study):

Exclusion Criteria. 1) Current or past Axis I DSM-IV disorder based on the MINI; 2) Current or past history of substance abuse or dependence (excluding nicotine) based on history or positive urine toxicology; 3) Current unstable medical condition; 4) Any current neurological condition or medical condition that is known to affect pupillary function, mood/anxiety, or neurologic function generally; 5) Pregnancy based on Urine Pregnancy Test; 6) Women who are breast feeding; 7) Use of medications known to affect CNS function within 5 half-lives screening; 8) Use of magnet controlled or programmed devices such as pacemakers, programmable ventriculoperitoneal shunts, or vagal nerve stimulators.

10.9 * RESEARCH CONDUCTED ON PATIENT CARE WARDS: Do any study activities take place on patient care units at UCSF medical facilities: (REQUIRED)

○ Yes ◉ No

11.0 Recruitment and Consent

11.1 * RECRUITMENT METHODS: What kinds of methods will be used to identify potential participants for recruitment (check all that apply): (REQUIRED)

- ☐ Medical records review
- ☐ Recruitment registry
- ☐ Re-contact of participants from the investigators' previous studies
- ☐ Referrals from colleagues (attach the 'Dear Colleague' letter or other recruitment materials you will provide to colleagues)
- ☑ Referrals from the community / word of mouth
- ☑ Advertisements (flyers, brochures, radio or t.v. ads, posting on clinical research sites or social media, presentation of the study at community events/media, etc.)
- ☐ Online recruiting tool such as TrialSpark
- ☐ CTSI Recruitment Services unit
- ☐ Other method (describe below)

Attach your recruitment materials (e.g., flyers, ads, recruitment letter templates, email text, etc.) in the Other Study Documents section of the Initial Review Submission Packet Form.

11.3 DETERMINATION OF ELIGIBILITY: How, when, and by whom will eligibility for recruitment be determined:

Flyers are placed around the UCSF campus and on the clinicaltrials.gov providing basic study information and eligibility criteria. Potential subjects will contact the study coordinator who will conduct a brief phone screen to determine initial eligibility criteria prior to scheduling the in-person screening visit. If the subject meets pre-screening criteria, an in-person screening visit will be scheduled at which time the subject will undergo screening procedures in Dr. Krystal's laboratory conducted by a study clinician. Normal healthy control subjects will be recruited and, following signing of informed consent, screened in the laboratory for whether they meet inclusion/exclusion criteria by Dr. Krystal or other study clinician and a study coordinator trained by and working under the supervision of Dr. Krystal. Assessments carried out during this visit will include a medical, psychiatric, and medication history, physical examination, urine drug screen, pregnancy test, and MINI. Those meeting entry criteria will then undergo the Anxiety Task or Auditory Oddball Task (AOT) administered by Dr. Krystal or the study coordinator. Those with a statistically significantly greater pupil diameter response to the Anxiety Task or the cues for the rare vs common stimuli in the AOT will continue in the study and be scheduled for return visits.

Flyers will be placed around the UCSF campus and in non-investigator faculty offices.

11.4 * INITIATION OF CONTACT: Who initiates contact (check all that apply): (REQUIRED)

- [ ] Investigators/study team
- [ ] UCSF recruitment unit (e.g. CTSI Consultation Services)
- [x] Potential participant
- [ ] Other (explain below)

11.5 * HOW IS CONTACT INITIATED: (check all that apply): (REQUIRED)

- [ ] In person
- [x] Phone
- [ ] Letter / email
- [ ] Website or app
- [ ] Other (explain below)

Attach the telephone recruitment script in the Other Study Documents section of the Initial Review Submission Packet Form. If potential participants will initiate contact, attach the telephone screening script that will be used to provide more information about the study and determine if callers are eligible to participate.

11.6 RECRUITMENT PLAN: Based on the checkboxes you chose above, please provide a narrative describing your recruitment plan. We want to know:

- **Who is conducting the search for potential participants, and how?**
- **How are potential subjects being approached for recruitment? By whom, and when?**

If there will be more than one participant group (e.g. patients, healthy controls, caregivers, family members, providers, etc.), provide details about the recruitment plans for each group. (Recommended length - 100-250 words)

Normal healthy control subjects will be recruited from the local community using posted flyers or referred by word of mouth, this study is also listed on the clinicaltrials.gov website. Individuals responding to the flyers, word of mouth or posting on clinicaltrials.gov website will contact the study coordinator and undergo a brief phone screen (phone script attached). The coordinator will schedule the subject for the inperson screening visit if they meet basic eligibility criteria.

11.7 * CONSENT METHODS: How will permission to participate (i.e., informed consent) be obtained from each potential participant. If there will be multiple groups and different plans for consenting each, check all that apply. See the orange Help bubble to the right for more detailed guidance. Participants will (check all that apply): (REQUIRED)

- [x] Sign a consent form at the end of the consent discussion (signed consent)
- [ ] Provide online 'eConsent' using DocuSign or another E-Signature system
- [ ] Click through a link in a survey or email after reading about the study and then complete the study online (electronic consent)
- [ ] Be told about the study and be given a handout/information sheet and be asked if they agree to participate (verbal consent)

Complete the study activities and turn in materials, as in the case of a completed survey that is placed in a drop box or mailed to the study team (implied consent)

Not be able to provide consent and will have a family member consent for them, as in the case of a critically ill or unconscious patient (surrogate consent)

☐

☐ Not be able to provide consent (emergency waiver of consent - allowed for minimal risk research or greater than minimal risk research with an approved community consultation plan)

☐ Not know about the study, as in the case of chart reviews or observations of public behavior (waiver of consent)

☐ Other method (describe below)

Attach your consent form, information sheet, or electronic consent text in the Informed Consent Documents section of the Initial Review Submission Packet Form.

11.8 * CONSENT PROCESS: Describe the process for obtaining informed consent, including details such as who will have the consent discussion and when participants will be asked to sign the consent form in relation to finding out about the study: (REQUIRED) We encourage researchers to review our guidance on obtaining and documenting informed consent.

- **If there are multiple groups being consented differently, provide details about the consent process for each group.**
- **If you are relying on verbal or implied consent, provide details about how that will happen.**
- **For studies using online recruitment and consent or consent via mail, provide details here.**

Written Informed Consent will be obtained from each subject prior to enrollment into the study. The process of informed consent will be carried out so as to ensure that potential subjects are properly informed as to the purpose of the study and the potential risks and benefits that are known, or that can be reasonably predicted or expected. All potential subjects will first have the study described to them verbally. This will then be followed by giving those subjects who remain interested in participating a copy of the informed consent document to review. This will then be followed by an opportunity to ask questions and express concerns. The Investigator will retain the original copy of the Informed Consent Form signed by the patient, a duplicate will be provided to the patient. Only the consent form approved by the IRB will be used. Potential subjects who do not have the capacity to give legally effective consent will not be included in this study.

* It is important that the people obtaining consent are qualified to do so. Briefly describe the training and experience these individuals have in obtaining informed consent: **(REQUIRED)**

The study coordinator, Blakely Andrews, will obtain informed consent. Blakely Andrews has been involved in research for over 10 years and has over 4 years of experience obtaining informed consent. The PI may also obtain consent and he has 25 years of experience consenting subjects in clinical research studies.

11.9 * CONSENT COMPREHENSION: Indicate how the study team will assess and enhance the subjects' understanding of study procedures, risks, and benefits prior to signing the consent form (check all that apply): (REQUIRED) Tip: Review the Consent Comprehension - Learning Notes in the Help bubble at the right for specific questions that can be asked to assess comprehension, consider using the UCSF Decision-Making Capacity Assesment Tool, and review our guidance on obtaining written or verbal informed consent for more detail on how to conduct the assessment.

☑

☐ The study team will engage the potential participant in a dialogue, using open-ended questions about the nature of the study or the experimental treatment, the risks and benefits of participating, and the voluntary nature of participation

Potential participants will be asked or shown a series of questions to assess their understanding of the

study purpose, procedures, risks and benefits, as well as the voluntary nature of participation (especially appropriate when the consent process happens online or through a mobile health app)
Other method (describe below):

Provide details of the other approaches that will be used, if using another method to assess comprehension:

11.13 TIME: What is the estimated time commitment for participants (per visit and in total):

Estimates for the R21 portion of the effort are included here:

For enrolled subjects 1-30, there are up to three total visits each scheduled 1 week apart. Screening procedures will take place at the first visit and will be combined with study procedures if the subject passes screening. The first visit will take 2 hours and the remaining 2 study visits will take 1.5 hours each for a total study committment time of 5 hours.

For the last 10 enrolled subjects, there are four total visits scheduled 1 week apart: Screening + 3 study visits. Screening will take between 1-1.5 hrs and the remaining 3 study visits will take 2-2.5 hrs each for a total study committment time of 7-9 hours.

IMPORTANT TIP: Ensure this information is consistent with the information provided in the consent form.

12.0 Risks and Benefits

12.1 RESEARCH-RELATED RISKS: Check if your study involves any of these specific research-related risks to participants that may need to be disclosed in the consent form:

- [ ] For interventional studies, risk that the regimen may be more harmful or less effective than other available interventions
- [ ] Risks associated with radiation exposure for imaging studies specifically for research purposes
- [ ] Risks associated with the administration of contrast agent for imaging studies
- [ ] Risks associated with withholding of treatment or discontinuation of current treatment (e.g., washout period is required by the study protocol)
- [ ] For randomized, placebo-controlled trials, possible temporary or permanent health consequences from the deprivation of effective therapies during the placebo administration period
- [ ] For studies involving a sham surgical procedure, the risk that participants may experience increased morbidity without the possibility of benefit
- [ ] Risks associated with modification or extension of a surgical procedure primarily for research purposes (e.g. risks associated with prolonging anesthesia, time in the operating room, etc.)
- [x] Risk of pain or physical discomfort caused by the research intervention
- [x] Possible personal discomfort due to sensitive topics (stress, embarassment, trauma)

12.2 RISKS: Describe any anticipated risks and discomforts not listed above:

There are no more than minimal medical or psychological risks associated with this research.

tDCS. Commonly observed adverse effects of tDCS are that skin irritation may occur at the site of the tDCS electrodes. tDCS may also cause minor adverse effects such as headache.

Pupillometry. Pupillometry is a minimal risk procedure and entail wearing eye glasses and potential discomfort of wearing the eyeglasses can occur with this procedure. Every effort will be made to maintain confidentiality, however this cannot be guaranteed.

Anxiety Task. Discomfort may be felt when determining the level of the "buzz" stimulus. We will start with a low level of "buzz" and step up gradually until the patient reports a level 7 for "annoying". The stimulus is meant to be "highly annoying" but not painful. At any time the patient reports pain, we will

decrease the "buzz" stimuli to the patient's level of comfort, as they self-report "annoying" but not "painful" level. The patient may stop at any time or have the stimulus reduced at any time. The number of stimulations delivered will be limited to 10 per 12 minute trial (stimulation associated with either the high or low tone). Parts of the task may become boring or repetitive. Efforts will be made to limit the number of trials administered per visit to minimize subject boredom and discomfort, while ensuring that adequate amounts of data are being collected.

Inhalation of 7.5% CO2. The primary adverse effect of 7.5% CO2 inhalation is the induction of Acute Fear which is also the reason that it is being carried out in this study. The fear is generally well-tolerated and resolves within roughly 10 minutes of the end of inhalation. A small percentage of subjects report increased sweating, tremor, tension, and tight muscles during or shortly after inhalation which is generally well tolerated. A gradual rise in blood pressure and pulse with a final systolic blood pressure rise of approximately 18 points, diastolic blood pressure rise of approximately 3 points, and heart rate elevation of approximately 8 points occurs with CO2 gas as compared to when subjects received "air" inhalation. In rare circumstances severe anxiety could be elicited. There is no evidence that repeated inhalations increases the risks of severe anxiety in response to inhalation testing or in the year following the inhalations. Several studies have evaluated the effects of repeated inhalations with 7.5% CO2 and higher percentages of CO2 and not found evidence that there is an increase in fear elicited or an increase in adverse effects with repeated exposures (Poma et al., 2005; Verburg et al., 1998). In addition, a group of healthy non-anxious subjects undergoing repeated exposure to 20% CO2 inhalation (N=155) were followed for up to a year and compared to a group of healthy non-anxious control subjects who breathed room air (N=56) and there was no evidence that the exposures to 20% CO2 increased the risk for anxiety /panic during the year of follow-up (Prenoveau et al., 2006).

ECG. Skin irritation from the ECG electrode pads or pain when removing the pads is a possible risk.

12.3

MINIMIZING RISKS: Describe the steps you have taken to minimize the risks/discomforts to subjects. Examples include:

- **designing the study to make use of procedures involving less risk when appropriate**
- **minimizing study procedures by taking advantage of clinical procedures conducted on the study participants**
- **mitigating risks by planning special monitoring or conducting supportive interventions for the study having a plan for evaluation and possible referral of subjects who report suicidal ideation**

This investigation has been designed to minimize the risks and discomfort incurred by study participants. Efforts will be made to reduce inconvenience to participants by scheduling assessment and experimental sessions at times that are most convenient to them. There will be no inclusion of vulnerable populations in this project (e.g., no children; mentally impaired persons; prisoners). To protect women of reproductive potential from risk, pregnant women, women who are breast feeding, or those who plan to become pregnant during the study will be excluded from study enrollment. For women of childbearing potential, a urine pregnancy test will be conducted, and must be negative before their entry into this study. If sexually active, women must agree to use appropriate contraceptive measures for the duration of the study. Medically acceptable contraceptives include: (1) surgical sterilization, (2) approved hormonal contraceptives
(such as birth control pills, Depo-Provera, or Lupron Depot) in combination with a barrier method,
(3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Women participants will be instructed to inform their study doctor immediately if they become pregnant during the study at which point participation in the study will end. The study doctor will then track the pregnancy and report the outcome to the Institutional Review Board (IRB). Adverse events will be monitored at each experimental session and standard procedures will be followed whenever an adverse event is recorded. In the event that a participant finds the screening interviews and questionnaires disturbing, the PI will be available to speak with the participant. The Study Coordinators will be trained by the site PI to handle personal material with confidentiality and sensitivity.

tDCS. Multiple steps will be taken to decrease the risks of tDCS. This includes using an electrical dose titration procedure with ongoing adverse event assessment and subject self-rating of discomfort which will guide whether dose increases occur in order to minimize discomfort and risk. This will also allow us to meet a goal of administering a dosage that is the minimum electrical dosage that engages our target to minimize risk. Also, because the

risks of tDCS which we propose to administer are not well characterized we plan to administer treatment for relatively brief periods (up to 10 minute stimulation sessions) and not administer treatments that have an impact on our target neural circuitry as indicated by pupillometry more frequently than weekly. Further, we may monitor ECG and breathing throughout and after all tDCS treatments to further minimize risks. Subjects will also be instructed to indicate if they have pain or discomfort and treatment will be stopped immediately if requested by a subject. Also, electrode sites will be checked for any skin abrasions prior to each treatment, as the presence of these increases the risk of skin burns. Treatment is not given if there are skin abrasions at the electrode sites. We will also carefully monitor subjects for adverse events after every stimulation with the SAFTEE tool and specifically ask them about the presence of the following side effects: itchiness, dizziness, lightheadedness, blurred vision, or headache. If any of these are answered positively, the duration of the symptom/s will be monitored and if it does not dissipate within an hour, which is typical of of the symptom/s will be monitored and if it does not dissipate within an hour, which is typical of tDCS, the participant will be assessed by a medical practitioner and appropriate care provided.

Pupillometry. In order to minimize risks of pupillometry, sessions will be kept as short as possible and there will be a study physician with all subjects during the procedure. Subjects will be assessed for adverse events and if they are detected, appropriate care will be made available.

7.5% CO2 Administration. In order to minimize risks of CO2 during each 20-min inhalation period, ECG monitoring and recording will occur continuously using a 12-lead ECG (Mortara Instruments) and breathing will be carefully monitored and recorded using pneumotachograph /integrator and data acquisition systems (Hans Rudolph). Skin conductance measures and breathby-breath changes in %CO2 will be monitored continuously and recorded using a CO2 sensor connected to a data acquisition system (Hans Rudolph, SmartLab unit). Further, two members of the study team including 1 study physician will remain with the participant constantly during inhalations as a safety measure. Participants will be able to terminate the inhalations at any point and will remain in the testing room until a study physician determines that it is appropriate for them to leave based on an examination. If adverse events are detected, appropriate care will be made available.

Anxiety Task. Efforts will be made to limit the number of trials administered per visit to minimize subject boredom and discomfort, while ensuring that adequate amounts of data are being collected. The subjects will be allowed rest periods between trials to minimize fatigue, they may also elect to terminate testing at any time. Comfort level for the irritating stimulus is determined prior to testing and set for each individual at their own comfort level. Before the anxiety task begins, the level of "annoying buzz" will be determined for the subject based on their verbal responses. First, a low level "buzz" (set at 5V) will be presented through stimulation generated to the ring and pinky fingers of the subject, using the BIOPAC STM-200 Stimulator (duration of less than 0.5 seconds) by the researchers. The subject will be asked to report on a scale of 0 (not at all annoying) to 10 (extremely annoying), how the stimulus feels. The presentation of the "buzz" will increase in increments of 5-10V (with a maximum of 100V) until the subject reports a level 7 for annoying. The purpose of this "annoying buzz" is to be highly annoying, but not to provoke pain. When the subject states the stimulus feels at a level "7" for highly annoying, the "buzz" settings will be set at this voltage.

Protection of Confidentiality will be accomplished by assigning each participant a distinct research code number and using this code number rather than the person's name on all documents and electronic data acquired from that individual. Data acquired from all participants will be kept in locked files at the study site and only this project's staff will have access to these files. When data are analyzed the data sets will include only participants' research code numbers as identifiers. No names or other unique identifiers will be included in any of the data sets used in the planned analyses of this project.

12.4 RESOURCES: Describe the resources in place to conduct this study in a way that assures protection of the rights and welfare of participants: These resources typically include appropriately trained and qualified personnel (in terms availability, number, expertise and experience), funding, space, equipment, and time to devote to study activities. Depending on the nature of the research study, investigators should consider the proximity or availability of critical resources that may be essential to the safety and welfare of participants, such as

the proximity of an emergency facility for care of participant injury
availability of psychological support after participation resources for participant communication, such as language translation services

Resources in place to conduct this study in a way that assures the protection of the rights and welfare of participants include:

1) all personnel involved in the study, which include the PI, Study Coordinators and Study Clinciians will all be appropriately trained and qualified. The PI has extensive experience as a PI of clinical research studies including studies involving tDCS and other brain stimulation modalities. He also has extensive experience training Study Physicians and Project Coordinators who have safely and effectively completed research projects;
2) Adequate funding from NIMH is available for completion of the study
3) Sufficient space for the successful completion of the study is available for carrying out the study at Langley Porter Psychiatric Institute
4) The necessary equipment is available for successful completion of the study
5) The PI, Study Coordinator, and Study Clinicians have the time available to successfully complete this study

12.5 * BENEFITS: (REQUIRED) Note: These are the benefits that the IRB will consider during their review.

They are not necessarily appropriate to include in the consent form.

Possible immediate and/or direct benefits to participants and society at large (check all that apply):

- [ ] Positive health outcome (e.g. improvement of condition, relief of pain, increased mobility, etc.)
- [ ] Closer follow-up than standard care may lead to improved outcomes or patient engagement
- [ ] Health and lifestyle changes may occur as a result of participation
- [ ] Knowledge may be gained about their health and health conditions
- [x] Feeling of contribution to knowledge in the health or social sciences field
- [ ] The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children
- [ ] Other benefit (describe below)
- [ ] None

12.6 RISK TO BENEFIT RATIO: Explain why the risks to subjects are reasonable in relation to anticipated benefits, if any, to the participant or society:

Acute fear occurs with many of the anxiety disorders when affected patients are exposed (including imagining or remembering) to fear evocative stimuli, such as to the object of their phobia, a trauma reminder etc. Although epidemiologic data do not exist specifically for Acute Fear, it can be assumed that it is an extremely widespread problem as anxiety-related disorders are the most prevalent class of psychiatric conditions, affecting approximately 18% of adults. Despite the existence of non-medication therapies and pharmacotherapy for addressing this problem many individuals fail to respond to treatment. Further, no treatments exist that have been developed specifically to address Acute
Fear. Accomplishing the aims of this proposal will advance our understanding of the mechanisms of Acute Fear and represents a step towards developing a treatment specifically for this common condition which has the potential to improve the lives of many individuals who suffer from this type of difficulty. These benefits to society outweigh the risks of the study outlined in the previous sections and taking into account the steps being taken to minimize those risks.

13.0 Data and Safety Monitoring Plan

13.2 * DATA AND SAFETY MONITORING PLAN: (REQUIRED)

All greater than minimal risk studies are required to provide a plan. Lack of an adequate plan is one of the most common reasons why IRB approval is delayed.

-

Instructions:

Describe the plan for monitoring data quality and participant safety. Key areas that should be included in the plan are:

An explanation of the plan to monitor data collection, study progress, and safety
A description of who will perform the monitoring and at what frequency (e.g., the PI only, a contract research organization, a Data and Safety Monitoring Board or Data Monitoring Committee, etc.)
The type of data and events that will be reviewed (e.g., adverse events, breaches of confidentiality, unanticipated problems involving risk to participants or others, unblinded efficacy data, etc.)
Procedures and timeline for communicating monitoring results to the UCSF IRB, the study sponsor, and other appropriate entities
Assurance that the research team will adhere to the **UCSF IRB reporting requirements**

As appropriate:

- A plan for conducting and reporting interim analysis
- Clearly defined stopping rules
- Clearly defined rules for withdrawing participants from study interventions

Because of the novel nature of the proposed work and that the adverse effects profile of the form of tDCS we propose to study is not well-documented, we have set up a Data and Safety Monitoring Board (DSMB) for both the R21 and R33 phases of the proposed effort. The individuals who serve on the DSMB were chosen in conjunction with NIH Program staff and have extensive experience conducting clinical trials and are highly familiar with the proposed methodology. The DSMB will convene every 6 months to review ongoing study procedures, discuss AEs and other safety issues, and to evaluate ongoing methods for maintaining data integrity and confidentiality. They will be provided with a summary of all AEs, outcome data, progress data and subject ratings of treatment tolerability prior to each meeting. They will play a critical role in working with the PI and NIH Program to assess whether the "Go-No-Go" criteria are met for proceeding to the R33 phase. If a decision is made to proceed, they will then monitor the R33 study. Should the DSMB members develop any concerns on the basis of information provided to them by the PI, they may request to examine hard or electronic copies of the participants' research records or other information. In transferring information to the DSMB participants' identities will be protected by transferring only data that are de-identified (hard copies) and/or encrypted (electronic data). In considering the frequency of meetings, we have tried to strike a proper balance between maintaining participant safety and the integrity of the study, and the consequent time and workload. Traditionally, DSMBs convene once a year. However, given the novel nature of this trial and that the risks of the form of tDCS we are administering are not well documented it was felt that every 6 month meetings were appropriate. After each meeting the DSMB will compile the information gained from the monitoring activities and subsequently prepare a report summarizing findings. Also included in the report is their recommendation to continue or discontinue the study. This report is completed and delivered to the NIH and the PI. If the DSMB concludes that the study should be terminated, this opinion will be conveyed to the UCSF business officials as well in the case of this latter type of recommendation. Subsequently the PIs, appropriate business officials at UCSF, and NIH Program will likely discuss the matter further before a final decision regarding study termination is made.

Local Monitoring of Subjects, Rules for Withdrawing Participants from Study Interventions, and Safety Stopping Rule: All subjects who undergo tDCS treatments will be carefully monitored locally by one of the study physicians. A study physician will be in the room with all subjects when any study procedures are carried out. There will be close monitoring of the tolerability of each of the tDCS electrode configurations studied. In order to determine the tolerability of particular tDCS electrode placement and electrical stimulus intensities, subjects will rate their discomfort immediately after each tDCS stimulus on a 5-point Likert scale that has been widely used to assess the tolerability of procedures including colonscopy, nasogastric tube insertion, burn dressing application, and orthodontic procedures. The anchors are: 0="No Discomfort", 1="Minimal Discomfort", 2="Mild Discomfort", 3=" Moderate Discomfort", and 4="Severe Discomfort". We employ a cutoff of no more 2 as an indicator of acceptable tolerability. We will employ the following stopping rule for each tDCS configuration test: "If any tDCS electrode configuration is rated at 3 or higher by 3 subjects, all testing with that electrode configuration will cease." In addition, if there is an SAE consisting of the development of new neuropsychiatric symptoms, the study will be halted until the cause of the symptoms is ruled not to be due to the study and, if such an event is determined to be related to the study, the study will not be restarted until modifications to the study methods are made that reduce the risk of such an event recurring based on a review and approval by the DSMB. Any subject who rates tolerability as 3 or greater for any electrode configuration will be withdrawn from further participation. Subjects will be informed that, at any time, they may request to the study physician that study procedures stop and this will occur. This includes that they will specifically be told that they should indicate if they would like tDCS stimulation to

stop during stimulation and it will cease and that they should indicate if they would like to stop CO2 inhalation during the CO2 inhalation procedure and that procedure will immediately be terminated.

Plan for Conducting and Reporting Interim Analysis and Stopping Rule

The study structure is such that there will be 4 cohorts of subjects each consisting of 10 subjects. Each of the first 3 cohorts will be stimulated with a different tDCS electrode configuration to determine if we can find one which is tolerable and inhibits locus coeruleus activity (as indicated by inhibition of a pupil dilatory response). After each cohort we will carry out an interim analysis to determine if this was the case (80% had tolerability ratings of 2 or less and there was statistically significant inhibition of the pupillary response to the anxiety task or auditory oddball task). Each of these interim analyses will be reported to the DSMB. If after the 3 cohorts are completed and if none of the 3 tDCS configurations tested meet the success criteria, then the study will cease. If one of the tDCS configurations meets the success criteria then an additional 10 subjects will be run using the successful tDCS configuration and using 7.5% CO2 instead of the anxiety task or auditory oddball test to elicit a pupillary response.

13.3 * DATA AND SAFETY MONITORING BOARD (DSMB): Will a Data and Safety Monitoring Board (DSMB) be established: (REQUIRED)

Yes

No

13.4 DSMB DETAILS: Provide details from the DSMB's charter, including meeting frequency, and affiliations and qualifications of members: If the DSMB has not yet been established, submit these details to us as they become available.

The DSMB will convene every 6 months to review ongoing study procedures, discuss AEs and other safety issues, and to evaluate ongoing methods for maintaining data integrity and confidentiality. They will be provided with a summary of all AEs, outcome data, progress data and subject ratings of treatment tolerability prior to each meeting. In transferring information to the DSMB participants' identities will be protected by transferring only data that are de-identified (hard copies) and/or encrypted (electronic data). After each meeting the DSMB will compile the information gained from the monitoring activities and subsequently prepare a report summarizing findings. Also included in the report is their recommendation to continue or discontinue the study. This report is completed and delivered to the NIH and PI. If the DSMB concludes that the study should be terminated, this opinion will be conveyed to the UCSF business officials as well. In the case of this latter type of recommendation. Subsequently the PIs, appropriate business officials at UCSF, and NIH Program will likely discuss the matter further before a final decision regarding study termination is made. The members of the DSMB are: William McDonald MD (Chairman), Professor of Psychiatry, Emory University who has extensive experience in carrying out research studies involving BrainStimulation therapies; William Coryell, MD, Professor of Psychiatry University of Iowa who has extensive experience in carrying out studies employing pupillometry in assessing psychiatric disorders; and Doug Case, Ph.D., Professor of Biostatistics at Wake Forest University who has extensive experience in Biostatistics.

14.0 Confidentiality, Privacy, and Data Security

14.1 PROTECTING PRIVACY: Indicate how subject privacy will be protected:

- [x]
- [x] Conduct conversations about the research in a private room
- [x] Ask the subject how they wish to be communicated with – what phone numbers can be called, can messages be left, can they receive mail about the study at home, etc.
- [ ] Take special measures to ensure that data collected about sensitive issues do not get added to their medical records or shared with others without the subject's permission Other methods (describe below)

14.2 SENSITIVE DATA: Do any of the instruments ask about illegal or stigmatized behavior:

(•) Yes ( ) No

IMPORTANT NOTE: Indicate in the consent form what kinds of sensitive information will be collected.

14.3 CONSEQUENCES OF A LOSS OF PRIVACY OR CONFIDENTIALITY: Could a breach of privacy or confidentiality result in any significant consequences to participants, such as criminal or civil

liability, loss of state or federal benefits, or be damaging to the participant's financial standing, employability, or reputation:

Yes No

14.4 EXTRA CONFIDENTIALITY MEASURES: Explain any extra steps that will be taken to assure confidentiality and protect identifiable information from improper use and disclosure, if any:

14.5 * REPORTABILITY: Do you anticipate that this study may collect information that State or Federal law requires to be reported to other officials, such as elder abuse, child abuse, or threat to self or others: (REQUIRED)

Yes No

14.6 CERTIFICATE OF CONFIDENTIALITY: Will this study obain a Certificate of Confidentiality:

○ Yes ◉ No

14.7 SHARING OF RESEARCH RESULTS: Will there be any sharing of EXPERIMENTAL research test results with subjects or their care providers:

○ Yes ◉ No

14.8 * IDENTIFIERS: Will any personal identifiers be collected: (REQUIRED)

◉ Yes ○ No

Check all the identifiers that may be included:

- ☑ Names
- ☑ Dates
- ☐ Postal addresses
- ☑ Phone numbers
- ☐ Fax numbers
- ☐ Email addresses
- ☐ Social Security Numbers*
- ☐ Medical record numbers
- ☐ Health plan numbers
- ☐ Account numbers
- ☐ License or certificate numbers
- ☐ Vehicle ID numbers
- ☐ Device identifiers or serial numbers
- ☐ Web URLs
- ☐ IP address numbers
- ☐ Biometric identifiers
- ☐ Facial photos or other identifiable images
- ☐ Any other unique identifier

* Could study records include *ANY* photos or images (even 'unidentifiable' ones): **(REQUIRED)**

○ Yes ◉ No

14.9 DATA DISCLOSURE: Will identifiable information be shared with outside groups:

○ Yes ◉ No

14.11 * DATA COLLECTION AND STORAGE: (check all that apply): (REQUIRED)

Collection methods:

- ☑ Paper-based (surveys, logs, diaries, etc.)
- ☐ Electronic case report forms (CRFs), such as OnCore or another clinical trial management portal
- ☐ Web-based online surveys or computer-assisted interview tool
- ☐ Mobile applications (mobile or tablet-based)
- ☐ Wearable devices
- ☐ Audio/video recordings

☐ Other:

* Data will be collected/stored in systems owned by (check all that apply): **(REQUIRED)**

☑ UCSF
☐ SF VAMC
☐ Amazon (Amazon Cloud)
☐ Other academic institution
☐ 3rd party vendor (business entity)
☐ Other (explain below)

14.12 DATA SECURITY: Indicate how data are kept secure and protected from improper use and disclosure (check all that apply): NOTE: Whenever possible, do not store subject identifiers on laptops, PDAs, or other portable devices. If you collect subject identifiers on portable devices, you MUST encrypt the devices.

☐ Data are stored securely in My Research
☑ Data are coded; data key is destroyed at end of study
☑ Data are coded; data key is kept separately and securely
☑ Data are kept in a locked file cabinet
☑ Data are kept in a locked office or suite
☑ Electronic data are protected with a password
☑ Data are stored on a secure network
☐ Data are collected/stored using REDCap or REDCap Survey
☐ Data are securely stored in OnCore

14.13 * DATA SECURITY: Confirm below that you will keep data confidential: (REQUIRED) I will keep any data sets that include identifiers secure and protected from improper use and disclosure by using methods such as:

- **Physical Security – Keeping data in locked file cabinets, locked offices, locked suites, and physically securing computers and servers.**
- **Electronic Security – Following UCSF minimum security standards for electronic information resources, which includes (but is not limited to): not storing identifiers on portable devices like laptops or flash drives if they are unencrypted, encrypting portable devices, and storing data in password-protected files and on secure networks.**

◉ Yes

14.15 HIPAA APPLICABILITY: Study data will be:

☐ Derived from the Integrated Data Repository (IDR) or The Health Record Data Service (THREDS) at SFGH
☐ Derived from a medical record (e.g. APeX, OnCore, etc. Identify source below)
☐ Added to the hospital or clinical medical record
☐ Created or collected as part of health care
☑ Obtained from the subject, including interviews, questionnaires
☐ Obtained ONLY from a foreign country or countries
☐ Obtained ONLY from records open to the public
☐ Obtained from existing research records
☐ None of the above

15.0 Financial Considerations

15.1 * PAYMENT: Will subjects be paid for participation, reimbursed for time or expenses, or receive any other kind of compensation: (REQUIRED)

(•) Yes ( ) No

15.2 PAYMENT METHODS: Subjects payment or compensation method (check all that apply):

Payments will be (check all that apply):

- [x] Cash
- [x] Check
- [x] Gift card
- [ ] Debit card
- [ ] UCSF Research Subject Payment Card
- [ ] Reimbursement for parking and other expenses
- [ ] Other:

15.3 PAYMENT SCHEDULE: Describe the schedule and amounts of payments, including the total subjects can receive for completing the study:

- **If there are multiple visits over time, explain how payments will be prorated for partial completion**
- **If deviating from recommendations in Subject Payment Guidelines, include specific justification below**

Participants will be provided monetary compensation to cover the time and effort they will invest completing the various study procedures. All but the last 10 subjects will receive up to $150 for completing the study which involves a screening session plus two visits. The last 10 subjects will receive $200 for completing the study, which involves a screening session plus three visits ($50 per visit) where tDCS will take place.

15.4 COSTS TO SUBJECTS: Will subjects or their insurance be charged for any study activities:

( ) Yes (•) No

16.0 Qualifications of Key Study Personnel

16.1 **NOTE: This information is required and your application will be considered incomplete without it. If this study involves invasive or risky procedures, or procedures requiring special training or certification, please identify who will be conducting these procedures and provide details about their qualifications and training. Also identify each person who will be involved in the consent process. Click the orange question mark for more information and examples.** **Under qualifications, please include:**

- **Academic Title**
- **Institutional Affiliation (UCSF, SFGH, VAMC, etc.)**
- **Department**
- **Certifications**

November, 2015 - NEW Definition of Key Study Personnel and CITI Training Requirements:

UCSF Key Study Personnel include the Principal Investigator, other investigators and research personnel who are directly involved in conducting research with study participants or who are directly involved in using study

participants' identifiable private information during the course of the research. Key Personnel also include faculty mentors/advisors who provide direct oversight to Postdoctoral Fellows, Residents and Clinical Fellows serving as PI on the IRB application. **The IRB requires that all Key Study Personnel complete Human Subjects Protection Training through CITI prior to approval of a new study, or a modification in which KSP are being added. More information on the CITI training requirement can be found on our website.**

Dr. Krystal, Andrew MD	Dr. Krystal will be responsible for overseeing all aspects of the proposed study. This includes training all personnel who will be involved in the study. Dr. Krystal will train and oversee the Project Coordinator who will along with Dr. Krystal will be obtaining informed consent.		Ray and Dagmar Dolby Distinguished Professor of Psychiatry Executive Vice Chairman of Psychiatry for Langley Porter Psychiatric Institute (Research) Department of Psychiatry UCSF Board Certified in Psychiatry, Sleep Medicine, EEG and Clinical Neurophysiology He has more than 25 years of experience being the PI of clinical research studies.
Andrews, Katherine B	K. Blakely Andrews is the study coordinator and responsible for oversight, protocol management, screening/eligibility determination, obtaining three consent, performing	Blakely Andrews has completed her study BA and has served as a research study coordinator for over years with experience in and data collection.	informed consent and carrying out study procedures. Training in informed consent specifically for this study and in study procedures will

		be performed prior to study initiation.
Dr. Seritan, Andreea L MD, MD	Dr. Seritan may be present during study visits serving as clinician.	Dr. Seritan is a licensed psychiatrist. a study
Marton, Tobias F, MD/PhD	Dr. Marton may be present during study visits serving as study clinician.	Dr. Marton is a licensed psychiatrist and possesses a a PhD in Neuroscience.
Dr. Scangos, Katherine MDPhD	Dr. Scangos may be present during study visits to observe or assist with clinical evaluations.	Dr. Lee is a resident in the Psychiatry department at UCSF.
Dr. Scangos is a licensed physician.		
Dr. Lee, Andrew MD PhD	Andrew (Moses) Lee may be present during study visits to run the tasks or assist with setup on subjects. He may also conduct data analysis.	

17.0 Other Approvals and Registrations

17.1 * ADMINISTRATION OF RECOMBINANT DNA: Does this study involve administration of vaccines produced using recombinant DNA technologies to human subjects (Help Link added Aug '15): (REQUIRED)

Yes No

○ ◉

17.2 * HUMAN GENE TRANSFER: Does this study involve human gene transfer (NOTE: Requires NIH Recombinant DNA Advisory Committee (RAC) review prior to IRB approval): (REQUIRED)

Yes No

○ ◉

17.4 OTHER APPROVALS: Indicate if this study involves other regulated materials and requires approval and/or authorization from the following regulatory committees:

Institutional Biological Safety Committee (IBC)

☐

Specify BUA #:

Institutional Animal Care and Use Committee (IACUC)

☐

Specify IACUC #:

Controlled Substances

☐

18.0 End of Study Application

18.1 End of Study Application Form

To continue working on the Study Application: Click on the section you need to edit in the left-hand menu. Remember to save through the entire Study Application after making changes. If you are done working on the Study Application: Important: Before proceeding, please go back to Section 4.0 Initial Screening Questions and Save and Continue through the form to make sure all the relevant sections and questions have been included. If you've changed any answers since

you started, the branching may have changed. Your application will be incomplete and it will have to be returned for corrections. Once you are sure the form is complete, click Save and Continue. If this is a new study, you will automatically enter the Initial Review Submission Packet form, where you can attach consent forms or other study documents. Review the Initial Review Submission Checklist for a list of required attachments. Answer all questions and attach all required documents to speed up your approval.

The UCSF IRB wants your feedback about this new form. Please click the link to take a brief survey about the new application form.