Psychosis Recovery and Research Center

Prefrontal Cortical Engagement through Non-Invasive Brain Stimulation in Schizophrenia

Clinical Protocol: Version 5.0 BCM
Version Date: 4/12/2019

Principal Investigator:	Raymond Cho, MD
Study Coordinator:	Cristin Rodriguez
Population:	Target sample Size is 100, male female, early schizophrenia diagnosis
Number of Sites:	Two sites. Baylor College of Medicine is the coordinating center site and the Michael E. DeBakey VA Medical Center is a secondary site.
Study Duration:	2 years
Subject Duration:	2 weeks

SYNOPSIS

Cognitive deficits are a strong predictor of functional outcome in schizophrenia, yet poorly remediated by current treatments. Disturbances in dorsolateral prefrontal cortex (DLPFC) function underlie core impairments such as in cognitive control and thus represent a critical target for novel therapeutics. Initial studies indicate transcranial direct-current stimulation (tDCS) may be effective in reducing symptoms due to DLPFC dysfunction. While tDCS potentially represents an exciting, novel therapeutic advance, a number of basic questions should be addressed prior to conducting larger-scale clinical trials, including: verifying therapeutic target engagement, optimizing treatment parameters, and evaluating for meaningful clinical effects.

BACKGROUND

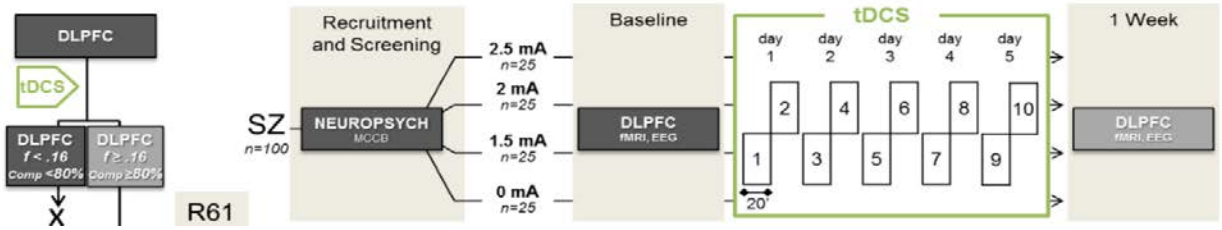
This protocol is supported by a NIMH award that is organized into two phases. The goals of the first (R61) and second (R33) phases are to demonstrate target engagement and then clinical effect by the therapeutic intervention, respectively. Specifically, the primary goal of the R61 phase is to employ multimodal imaging to explicitly test for the assumed DLPFC engagement (fMRI) and modulation of frontal gamma activity (EEG) by tDCS, investigate the optimization of tDCS application parameters, and confirm the tolerability of tDCS for schizophrenia patients, and will be the focus of this protocol. After confirming that this effect is driven by tDCS effects in a positive direction, the current strength that has the highest effect size and also meets >80% completion rate will be the one that is selected for the R33 phase, which will seek to demonstrate clinical effect by assessing clinical outcomes scales and observing improvements in cognitive control mediated by DLPFC and frontal gamma oscillation engagement.

A successful outcome of this study would provide tDCS the sound mechanistic, methodologic and clinical-relevance basis for more definitive testing in large-scale clinical trials as a highly innovative therapeutic intervention for cognitive impairments in schizophrenia.

OBJECTIVES AND HYPOTHESES

100 participants will undergo screening, and upon successful screening, be randomized to one of four treatment groups: 0mA (sham), 1.5mA, 2mA, and 2.5mA. Baseline measures of fMRI and EEG are taken before tDCS treatment. tDCS treatment is twice daily for five consecutive days. Following the last tDCS treatment, a posttest fMRI and EEG is conducted.

An overview of the study design is provided below:



Primary Objective

- To investigate engagement of the DLPFC and frontal gamma oscillations as targets of frontal tDCS application in early schizophrenia patients. We will index the modulating effects of tDCS on DLPFC activity using fMRI BOLD imaging and gamma oscillations with EEG recordings in the context of cognitive control task performance.

Secondary Objectives:

- To evaluate optimal strength (1.5 vs. 2.0 vs. 2.5 mA) in tDCS application for DLPFC engagement. Analogous to dose-finding in drug studies, we will conduct a parametric test for optimal current strength.
- To investigate the tolerability and feasibility of multi-session tDCS in schizophrenia. There is extensive evidence for tolerability of tDCS, confirmation for schizophrenia will be explicitly evaluated.

Hypothesis

The primary hypothesis to be tested in this study is observing positive modulations in fMRI BOLD signals in the DLPFC and EEG frontal gamma oscillations during a cognitive control task following frontal tDCS modulation. We hypothesize tDCS application at 2.5 mA will show greatest engagement of DLPFC and frontal gamma oscillations and that 80% of subjects will complete the full tDCS protocol.

OVERVIEW OF STUDY DESIGN

We aim to investigate transcranial Direct Current Stimulation (tDCS) as a novel therapeutic for cognition in psychosis. We will recruit 100 early phase schizophrenia patients with cognitive control deficits. A range of current strengths will also be explored, ranging from 1.5 to 2.5 mA in 0.5 mA increments. Thus, the subjects will be divided into four groups of N=25 for each of the tDCS current strengths including a sham stimulation (placebo) group.

We will recruit equal numbers of female and male participants. Subjects will have less than five years of treatment history and currently be on stable doses of second-generation antipsychotic medications for at least one month. Antipsychotic exposure history will be fully assessed and converted into standardized equivalents. The total duration of this study will be approximately 2 weeks. However, the majority of the study will be within a one week period.

Table 1: Overview of Study Design								
Procedure	**Screening**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Week 1**
Medical, Medication History, Demographics, Color-blind screening	X							
Urine Screen	X							
MRI Screening Form	X							
Clinical Assessments	X							
Cognitive Assessments	X							
fMRI		X						X
EEG		X						X
tDCS			X	X	X	X	X	
Tolerability Assessment			X	X	X	X	X	
Comprehension Assessment	X	X	X	X	X	X	X	X
Payment	$40	$75	$10	$10	$10	$10	$10	$75
Total								$240

Screening: Participants who provide written informed consent will undergo screening procedures and a review of the study eligibility criteria. At this visit the participant will complete the initial screening process, which includes detailed demographic information (including medication and treatment information), diagnostic information using the M.I.N.I diagnostic neuropsychiatric interview (M.I.N.I 7.0.2). Additionally, a cognitive assessment, MATRICS, will be conducted to assess level of cognitive functioning. Psychopathological ratings that are conducted include: the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Positive Symptoms (SAPS), the Scale for the Assessment of Negative Symptoms (SANS) the 7-point Clinical Global Impression (CGI) Scale, the Global Assessment of Functioning (GAF). If participants meet the inclusion/exclusion criteria (see section Subject Population), participants continue to next visit.

Day 1: Experimenters will perform baseline fMRI and EEG procedures. Cognitive effects will be evaluated to assess acute effects of tDCS compared to baseline and to evaluate persistence. Subjects will undergo MRI in order to assist localization of EEG data and provide independent and complementary correlates of tDCS effects.

Day 2- 6: During these visits, the participants will undergo two 20 minute daily tDCS sessions, separated by 1 hour, for 5 consecutive days. Tolerability assessment will be administered to gauge how tolerable the tDCS session for the participant. Comprehension assessment will be administered to gauge the patients understanding of the study and to ensure they still have informed consent.

Week 1: Experimenters will perform posttest fMRI and EEG procedures. Cognitive effects will be evaluated to assess effects of tDCS compared to baseline and to evaluate persistence. Subjects will undergo MRI in order to assist localization of EEG data and provide independent and complementary correlates of tDCS effects.

Payment:

Participants who park in the Greenpark parking garage will have their parking tickets validated. Parking will also be validated at the MRI location.

Participant will be compensated for their time, as follows:

Visit 1: $40 Visit 2: $75 Visit 3: $10 Visit 4:$10 Visit 5: $10 Visit 6: $10 Visit 7: $10 Visit 8: $75 Total: $240

A ClinCard will be used for study payments. Payments will be loaded onto the ClinCard within 48-72 hours of visit completion. The research study team will provide the participant with a handout about the ClinCard. The participants email address and/or cell phone number will be collected in the event they want email or text notification when payments are loaded to their ClinCard.

Baylor College of Medicine and Greenphire (ClinCard Company) have entered into an agreement which requires Greenphire to protect personal information.

The College will replace the participants ClinCard free of charge if their first card is lost or stolen. After that, there is a $7 ClinCard replacement fee. This replacement fee will be charged to the balance on the participants ClinCard at the time of replacement. The participants ClinCard has an expiration date. If their ClinCard expires while they are participating in this study, Baylor will provide the participant with a new ClinCard at no cost. For a period of three months following the participants final study visit, they may request replacement of an expired ClinCard at no cost.

Payments for research participation are considered taxable income per Internal Revenue Service (IRS) regulations. If the total amount of payment received by the participant, the participant's parent, guardian or legally authorized representative (LAR) reaches or exceeds $600 in a calendar year, Baylor College of Medicine will send an IRS Form 1099 to that person for tax purposes.

In order to issue the IRS Form 1099, Baylor will collect the participants first and last name, social security number, date of birth and home address. The name the participant provides should match the social security number. If the participant does not wish to provide a social security number, they can still participate in the study and decline all payment.

Study payments are considered income and may or may not affect government or public assistance benefit programs the participant or participant's parent, guardian or LAR may be participating in, such as SSI (Supplemental Security Income) or TANF (Temporary Assistance for Needy Families).

SUBJECT POPULATION

We will recruit 100 early phase schizophrenia patients with cognitive control deficits. We will recruit equal numbers of female and male participants across the Michael E. DeBakey VA Medical Center (MEDVAMC) and BCM. A range of current strengths will also be explored, ranging from 1.5 to 2.5 mA in 0.5 mA increments. Thus, the subjects will be divided into four groups of N=25 for each of the tDCS current strengths including a sham stimulation (placebo) group. We will recruit equal numbers of female and male participants. We have no hypotheses that relate to ethnicity or race. Minorities will be represented corresponding to or in slightly greater proportion to their prevalence in the Houston Metropolitan Statistical Area.

Inclusion Criteria**:**

a) ages 18-35 years;

b) within first five years of antipsychotic treatment;

c) on stable doses of antipsychotic medication for at least one month;

d) Clinically stable as defined by Clinical Global Impression−Severity scale (CGI−S) less than or equal to 4 (moderately ill);e) MINI 7.0.2 criteria for schizophrenia or schizoaffective disorder

Exclusion Criteria**:**

a) Mental retardation as defined by pre-morbid IQ by Wechsler Test of Adult Reading at screening <70 or Spanish Word Accentuation Test;

b) Significant head injury;

c) History of severe medical or neurological illnesses;

d) Pregnancy or postpartum (<6 weeks after delivery or miscarriage);

e) Inability to provide informed consent;

f) Significant color blindness that affects task performance;

g) Currently on benzodiazepines or mood stabilizers affecting GABA

h) Positive urine drug screen (excluding THC at baseline) or presence of substance abuse or dependence within 1 month;

Note: If a participant tests positive at Baseline for THC, they will not be automatically excluded. These individuals will be retested at the EEG/MRI appointment. During the EEG/MRI appointment, if they test positive for any substances they will not be allowed to complete the appointment and they will be withdrawn. The participants will be informed of this ahead of time.

Baylor College of Medicine Recruitment

Subjects will be recruited from the outpatient clinical programs at Baylor College of Medicine and other community psychiatric programs. These will include Ben Taub's psychiatric emergency room and inpatient and outpatient center and MHMRA. Primary clinicians at BCM will be notified of our research study. Potential subjects with a diagnosis of schizophrenia will be identified and initially approached through their primary clinician, who will ask patient's permission to be contacted by the research team. Upon obtaining patient's written permission, a staff member from the research team will contact the subject. We will also recruit participants through flyers in the community, newspapers, social media (such as facebook), and BCM's clinical trials website.

Additionally, we will recruit from The Menninger Clinic who are aware of our clinical and research program. In addition to The Menninger Clinic, we will recruit from their affiliate "The Gathering Place". At The Gathering Place, members there will be shown presentations about research and will be provided research staff contact information. Consent to contact forms will be left at the facility so that members of The Gathering Place may later be contacted by research staff. Additionally, advertisements approved by their administration may be left at the facility.

Michael E. DeBakey VA Medical Center Recruitment

All recruitment materials, consent forms, and Health Insurance Portability and Accountability Act of 1996 form will be approved by the MEDVAMC Research and Development Committee and the IRB prior to the beginning of the protocol. The study personnel will have certification of Human Subjects Research Training. Informed consent will be obtained prior to conducting any study procedures.

In-person recruitment will occur at Michael E. DeBakey VA Medical Center (MEDVAMC) and its related outreach clinics in the Houston area. Advertising materials will be posted in hospital bulletin boards and flyers/brochures will be distributed at VA events (e.g. VA Research Week Fair). To reach Veterans who do not visit the VA, recruitment flyers will be distributed on college campuses, community social media pages and newsletters, and at Veterans' Service Organizations (VSOs) events.

By pre-screening patients in CPRS, the research team can focus recruitment efforts on Veterans who are more likely to qualify for the study. Pre-screening involves interviewing the patient to check for inclusion/exclusion criteria. (Veterans who are referred or recruited through flyers may be pre-screened through CPRS chart review or over the phone).

Individuals who satisfy the pre-screen requirements will be mailed an invitation letter with information about the study. The letter will include an option to opt-out from being contacted about the study. Approximately two to three weeks after mail-outs, a study coordinator will follow-up with candidates who were sent invitation letters. Veterans who opted out will not be called. Additionally, psychiatrist will be contacted, for patients who have upcoming appointments, in order to obtain consent to contact from the patient.

Alternatively, participants will be recruited by information booths set up in the outpatient psychiatry clinic. Inpatient units of MEDVAMC will be an additional recruitment source; in the case that an individual within MEDVAMC's inpatient facility might be eligible for the study, staff will reach out to the patient's doctor to determine if the doctor feels the patient would be a good fit for the study and when the patient's discharge is predicted to be. With doctor approval, staff will speak with the patient at discharge to determine their interest and follow up at a later date.

Interested individuals will be scheduled to meet with the PI and/or a research team member to discuss the study's goals and procedures in detail. After meeting the PI/research team member, Veterans who wish to enroll will be scheduled to start the study. Meeting the PI/coordinator before enrolling in the study allows the individual extra time to consider his/her decision to participate and reduces the risk of coercion or undue influence.

When the participant is ready to enroll in the study, he/she will review the consent document and be given ample time to ask questions. Participants will also be reminded that participation is voluntary and will not affect their access to healthcare or benefits. A copy of the signed consent form will be given the participant. No study procedures (structured screening or testing) will commence prior to obtaining informed consent.

Recruitment Milestones

We plan to frontload recruitment with a target of 60 participants in the first year and the remaining 40 in year two. This strategy will leave time in year two to finalize analyses, address the transition criteria to the R33 phase, and prepare abstracts and manuscripts related to the R61 aims.

TREATMENT ALLOCATION AND BLINDING

Randomization, Blinding and Tolerability Assessments

Subjects will be randomly assigned to one of the three active tDCS (1.5 mA, 2.0 mA or 2.5 mA) or sham groups (N=25/group), under the constraint of group-level demographic and cognitive status matching. For robust blinding, we will coordinate three different teams of experimenters, responsible for 1) clinical/neuropsychological status evaluations; 2) tDCS application; and 3) EEG/fMRI recording and data analysis. Critical to our third aim, the second team will be responsible for assessing tolerability during the stimulation and general adherence to the stimulation sessions. We will employ a "triple-blind design" in the following manner to minimize unintended biases/confounds: randomized group assignment; automatic, computer control of the stimulator according to the encrypted subject's group; de-identified data analysis.

STUDY PROCEDURES

Overview: The Overview of Study Design table (Table 1) summarizes the frequency and timing of the clinical, imaging, treatments, and other exploratory measurements applicable to this study. Below lists in further detail all procedures involved in the study.

Interviews and Ratings

Cognitive Assessment: Participants will be interviewed in a dedicated room at the BCM Greenpark I building. The cognitive assessment tool that will be used is the MATRICS assessment. The full MATRICS battery targets the six cognitive domains (speed of processing; attention/vigilance; working, visual and verbal memory; reasoning and social cognition) identified as being disturbed in schizophrenia. The MATRICS battery takes approximately 1.5 hours.

Clinical Assessments: In addition to detailed demographic information (including medication and treatment information), we will obtain diagnostic information using the Structured Clinical Interview for DSM-V Disorders and/or the M.I.N.I diagnostic neuropsychiatric interview (M.I.N.I 7.0.2) at the discretion of the PI. Psychopathological ratings are conducted include: the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Positive Symptoms (SAPS), the Scale for the Assessment of Negative Symptoms (SANS), the 7-point Clinical Global Impression (CGI) Scale, the Global Assessment of Functioning (GAF). IQ will be assessed using the Wechsler Test of Adult Reading (WTAR) or the Spanish Word Accentuation Test for Spanish speaking patients.

Medical assessments: A medical history will be obtained from all participants.

Experimental Procedures

tDCS: Participants will undergo two 20 minute daily sessions, separated by 1 hour, for 5 consecutive days. All sessions will be hosted at the Greenpark One site. Identical electrode montages will be applied across all conditions/groups. Given the mechanistic emphasis of the study on target engagement and in order to map effects unambiguously, prefrontal stimulation will be applied in isolation. DLPFC involvement in cognitive control does not show consistent hemispheric lateralization and complex compensatory responses to unilateral stimulation are believed to underlie the variable responses observed in cognitive paradigms. Accordingly, we will stimulate left and right DLPFC simultaneously. This will be achieved by positioning two "active" anodic electrodes on the scalp, placed over F3 and F4 10-20 system electrode sites and two electrodes on the deltoid muscles. This montage was validated by computational models of current flow to robustly target DLPFC.

tDCS will be delivered by a constant-current multi-channel stimulator (NeuroMod tXES Stimulator, RGN, New Mexico, USA) through conductive-rubber electrodes placed in sponges saturated with saline (0.9% NaCl). Micro-processor-controlled current outflow, with independent impedances monitoring and voltage adjustments, will ensure the safe application of identical currents through PFC regions. For the active tDCS groups, constant

current will be applied at the specified level, with 20 sec fade-in and fade-out. The sham group will undergo identical procedures except for the stimulation (aside from the fade-in/fade-out) and will consist of brief (1 second) low current (0.11 mA) pulses every 10 seconds. This differs from sham procedures used in other studies in order to ensure a more reliable control condition.

Cognitive testing and EEG: Cognitive effects will be evaluated to assess acute effects compared to baseline and to evaluate their persistence. Subjects will be asked to do some simple tasks which will involve looking at a computer screen display (figures, symbols, numbers, letters, words or sentences) or listening to sounds through headphones (clicks, beeps, or words). The participant is asked to respond to the stimuli by pressing a response button. Stimuli will be presented on a computer screen using E-Prime (Psychological Software Tools, Pittsburgh, PA). Dependent variables will be reaction time, response, and accuracy collected via keyboard, joystick, button box or similar device and stored on a computer. The task will involve separate trials and trials are organized in blocks so that participants will be allowed to rest in between blocks. In each session, cognitive tasks will be presented on a computer screening using E-Prime (Psychology Software Tools, Pittsburgh, PA). EEG will be administered with concurrent high-density (64 channel) EEG acquisition (BrainAmp MRPlus, Brain Products, Munich, Germany) system. This system is CE certified.

MRI: Subjects will undergo MRI in order to assist localization of EEG data and provide independent and complementary correlates of tDCS effects. A technician will place the head-coil on the subject, which is like wearing a helmet. The subject will be asked position themselves on a platform that slides inside a large tube (the MRI machine). The subject will be asked to perform computer tasks while in the MRI scanner. These tasks maybe similar in nature to the ones performed during EEG. Participant will be given specific instructions before the session and again for each task before it begins. The scanning session will include both functional and structural MR images. MRI sequences will involve full brain scans - high-resolution structural T1 weighted sequence and functional EPI during task performance as in EEG. Resting state fMRI and DTI may also be acquired. Functional Magnetic Resonance Spectroscopy (MRS) may also be acquired.

Location of Study Procedures Across Sites:

Participants who are recruited through BCM will ONLY complete study procedures at BCM. The participants who are recruited through the MEDVAMC will complete consent and screening procedures at the MEDVAMC. While EEG and tDCS equipment are being acquired and set-up (both should be acquired at the MEDVAMC site approximately by November 2018), MEDVAMC participants will complete EEG and tDCS at the BCM Greenpark location as to not delay the participation of these subjects. The MEDVAMC participants will use the consent form in H-43556, which is specific to the VA and outlines the exact location of each of the procedures.

Once the EEG and tDCS equipment is fully functional at the MEDVAMC, an amendment will be made to the BCM and MEDVAMC protocols and consents indicating that EEG and tDCS will be taking place at the MEDVAMC for the Veterans. At that point, the Veteran participants will be able to complete the majority of the study procedures at the MEDVAMC, with the exception of fMRI. Due to scanner specificity, the fMRI portion of this study will remain at the BCM CAMRI location for the foreseeable future.

National Institute of Mental Health Data Archive (NDA)

Data from this study will be submitted to the National Institute of Mental Health Data Archive (NDA). NDA is a data repository run by the National Institute of Mental Health (NIMH) that allows researchers studying mental illness to collect and share deidentified information with each other. A data repository is a large database where information from many studies is stored and managed. Deidentified information means that all personal information about research participants such as name, address, and phone number is removed and replaced with

a code number. With an easier way to share, researchers hope to learn new and important things about mental illnesses more quickly than before.

During and after the study, the researchers will send deidentified information about participant's health and behavior to NDA. Other researchers nationwide can then file an application with the NIMH to obtain access to the deidentified study data for research purposes. Experts at the NIMH who know how to protect health and science information will look at every request carefully to minimize risks to participant privacy.

Participants may not benefit directly from allowing their information to be shared with NDA. The information provided to NDA may help researchers around the world treat future children and adults with mental illnesses so that they have better outcomes. NIMH will also report to Congress and on its web site about the different studies that researchers are conducting using NDA data. However, participants will not be contacted directly about the data they contributed to NDA.

Participants may decide now or later that they do not want to share their information using NDA. If so, research participants will need to contact the researchers who conducted this study and the researchers will tell NDA, which can stop sharing the research information. However, NDA cannot take back information that was shared before the participant changed their mind. More information about the NDA is available on-line at http://data-archive.nimh.gov.

ASSESSMENT OF RISK AND SAFETY

Clinical Assessments: Clinical and neuropsychological assessments are all performed by trained research personnel to reduce the risk of distress from psychiatric interviews and experimental procedures.

Confidentiality: Another potential risk is the possibility of loss of confidentiality in case information is lost or misplaced. All protected health information (PHI) will be kept in locked drawers or password protected storage on computers.

tDCS: Side effects associated with tDCS procedures include a tingling or itching sensation on the scalp. Very rarely, there may be heating and even burning of skin. The subject will be asked to provide feedback about the degree of comfort and will be able to speak with experimenters at all times. In the rare event the subject find the stimulation highly discomforting or intolerable, the stimulation will be promptly stopped. If the subject is unwilling to resume the protocol, they may withdraw from the study.

EEG: The electroencephalography (EEG) system is not FDA approved, but CE certified. It is a non-invasive procedure which may cause skin irritation from the placement of recording electrodes in less than 1% of people. Itchiness of scalp or redness because of electrode gel could result and has the same amount of risk as saline solution. The EEG is administered by trained research staff and can be stopped at any time if the subject becomes uncomfortable.

MRI: MRI is very safe, with no radiation or contrast media involved. The procedure has the same risk as a clinical MRI. The only risks of the procedure would be in the event that the patients have metal particles in their body, which if mobile could act as projectiles, or be mechanically activated or displaced if implants. These risks will be minimized using systematic procedures and well-trained technicians, with very careful screening for metal and implants prior to scanning. Claustrophobic reactions can make participation impossible for some subjects. History suggesting of a predisposition will be investigated. However discomfort could arise within the bore even

in absence of positive history. The technician will make sure the individual is comfortable before starting the imaging. During the MRI, the subject will hold onto a ball that sounds an alarm when squeezed and will be instructed to do so if he/she becomes uncomfortable during the procedure. If that happens, the technician will stop the scan to check on the participant.

Importantly, any unanticipated problems will be reported to IRB immediately (within 24 hours). The research team will meet on a weekly basis to review study safety issues, adverse events, data integrity and any other relevant study issues. Any significant concerns or issues during the conduct of the study will be immediately communicated to the study PI. In addition, we will immediately report all of the above to our Data and Safety Monitoring Board (DSMB).

Provision of Care to Research Participants and Risk Management

Study Discontinuation: Participants can be discontinued from the research protocol at the PI's discretion due to medical contraindications, intolerable adverse reactions, lack of adherence to study procedures, or clinical deterioration that places participants at risk.

Poor Adherence: If a participant misses one tDCS appointment, the PI will allow the participant to remain in the study as long as there are no further missed tDCS appointments. The missed tDCS appointment must be made up for with one additional visit for a total of 10 tDCS sessions, per protocol requirements. Non-adherent participants will be discontinued from the study.

Methods to Decrease Attrition: (1) Providing a subject remuneration totaling $240 for participant's time. (2) Offering flexibility in scheduling to work around school or work schedules (3) Snacks and refreshments at visits.

After-Care: Participants who complete the study and those who drop-out for any reason including lack of response or side effects are referred back to their usual providers.

STATISTICAL METHODS

Primary Objective: Dependent measures will be task condition-related differences in fMRI BOLD activation as measured through GLM and EEG oscillatory activity in the gamma band as analytically estimated by complex wavelet transformation. Group and time point differences will first be assessed with omnibus tests instantiated through the general linear model (e.g., repeated measures ANOVA) to determine the presence and direction of potential effects. Effects equivalent to $f \geq .16$ will be targeted. To determine the efficacy of the treatment conditions, we plan to conduct post-hoc comparisons of the post- minus pre-test differences between each active stimulation group and the sham stimulation group, as well as within each group between the post- and pre-test measures. The behavioral context of these changes will also be assessed by the Inc-Con difference in accuracy and reaction time in an analogous manner to fMRI and EEG measures.

Secondary Objective: Initial analytical targets will be identified concurrent with Aim 1. Polynomial trend analyses will be used to determine the dose-response curve to tDCS. To assess the degree of efficacy of each treatment, Cohen's d_Z, a measure of effect size similar to Cohen's d which also accounts for the covariance between measures, will be calculated within each group based on the difference between control-related activations from the pre- and post-test assessments with an ideal target of d_Z=.534 for fMRI BOLD activation and d_Z=.687 for EEG gamma synchrony (i.e., half the observed distance between patient and control measures based on preliminary data). As an exploratory analysis, we will also make use of the structural MRIs to create individualized head models of current strength in the DLPFC. Since the current strength, distribution and even polarity can vary considerably as a function of individual physiology and anatomy, such comparisons between the predictive value of the tDCS device's current output vs. the modeled current strength in relation to the fMRI

and EEG measures will be invaluable in informing future investigations of personalized treatment protocols and tDCS tolerability/safety.

Tertiary Objective: A target completion rate of 80% serves as our benchmark for assessing feasibility. No analysis is required - this benchmark will simply serve as the required threshold for starting the R33 phase.

R61 to R33 Phase Transition Criteria: Our 'Go/No-go' strategy for this transition will require an effect size of tDCS to be $f \geq .16$ for both DLPFC BOLD signal and frontal EEG gamma activity. After confirming that this effect is driven by tDCS effects in a positive direction, the current strength that has the highest effect size *and* also meets >80% completion rate will be the one that is selected for the R33 phase.

REGULATORY ETHICS COMPLIANCE

Investigator Responsibilities

The investigator is responsible for ensuring the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice, and applicable regulatory requirements. During the study the investigator will send the following documents and updates to the Baylor College of Medicine Institutional Review Board for their review and approval, where appropriate:

a) Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study contact)

b) Revision(s) to ICF and any other written materials to be provided to subjects.

c) Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable.

d) Reports of adverse events that are serious, unlisted/unexpected, and associated with the study protocol.

e) Deviations from or changes to the protocol to eliminate immediate hazards to the subjects.

f) Any other requirements of the IRB.

At the end of the study, the investigator will notify the IRB about the study completion.

Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF will be signed before performance of any study-related activity. The ICF that is used must be approved by the reviewing IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles with current ICH and GCP guidelines and applicable regulatory requirements. Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease.

The subject will be given sufficient time to read the ICF and the opportunity to ask any questions. After having obtained written consent, a copy of the ICF will be provided to the participant.

IRB approval will be sought from Baylor College of Medicine Institutional Review Board. Privacy and confidentiality will be maintained with a special number to be used to identify the subject in the study and only the investigator and his research staff will know their name.

Privacy of Personal Data

The clinical information obtained from subjects will be part of their study records and maintained at BCM in a facility with adequate safeguards for the protection of confidentiality. The research data will be collected and recorded using only arbitrary study IDs. All data will be kept in a secure area. Only the members of the research group will have access to the data files or to the master list for the codes (linking log form attached). For publication purposes, the patients will be designated only by codes. Our research team is in compliance with all HIPAA privacy guidelines. In summary, the potential risks for participants in this study will be minimized by careful medical and psychiatric evaluations and procedures, regular monitoring of subjects' clinical status, careful screening of subjects before the EEG and MRI scans and defined procedures for maintaining confidentiality.

Quality Control and Assurance

The study will be monitored by a Data Safety Monitoring Board (DSMB). The DSMB will independently review the protocol and consent documents, AEs, and outcome data as needed, for the proposed study. The DSMB will evaluate issues related to subject safety and the adequacy and integrity of accumulated data. The DSMB will meet once for every 20 subjects who have completed the study to review the study. Data reports will be prepared by Dr. Raymond Cho's study coordinator to support the work of the DSMB.

The study coordinator will create tables for the DSMB to review. The tables will include enrollment, demographic information by treatment arm, abnormal laboratory results, SAEs, and missing data. After each meeting, the DSMB will issue a memo documenting any action items for the team. Copies will be provided to the Baylor IRB upon request.

Dr. Raymond Cho's lab will conduct routine (bimonthly) reviews of consistency, reliability and accuracy of data collected for any paper records. Similar checks for any data in electronic form will also be conducted but in an automated fashion (e.g checking for accurate time/date stamps, file sizes etc.).

Stopping Rules: Participants must complete the 5 consecutive days of tDCS treatment within a maximum of 6 consecutive days. Appointments will be scheduled for 5 consecutive days however, if a participant misses an appointment we will only allow one day to be rescheduled. If the 5 sessions are not completed within the 6 days allotted the participant will be withdrawn from the study.

Confidentiality and Assured Data Transfer and Safety Monitoring

Data collected at the MEDVAMC are to be used in a multi-site study that combines MEDVAMC data with BCM data. Furthermore, the data will be disclosed to BCM, which is the coordinating center, where the data will be combined and analyzed for this study. Below are further details on the coordination of data between sites.

All physical research data that is collected at the Michael E. DeBakey VA Medical Center will be kept on site (2002 Holcombe Blvd, Houston TX 77030, room 6B-390). Data collected at the Baylor College of Medicine Greenpark I site will also be kept at that respective site (7515 Main Street, Suite 300, Room GP3. 303, Houston TX 77030). The research data collected at the MEDVAMC will be in a locked file cabinet in a locked room at the MEDVAMC campus (2002 Holcombe Blvd, Houston TX 77030, room 6B-390). Data collected at the Baylor College of Medicine Greenpark I site will also be locked in a file cabinet in a locked room (7515 Main Street,

Suite 300, Room GP3. 303, Houston TX 77030). All de-identified study data will be available only to personnel involved in the study through the use of access privileges and passwords.

Baylor College of Medicine will be the data coordinating center for this study. MEDVAMC research data will be entered into a database on site, and later transferred to the BCM location via encrypted drives. Electronic data will be located at the Baylor College of Medicine Greenpark I site (7515 Main Street, Suite 300). All records and samples will be coded and identified only by numbers. Information obtained from participants in this research, including answers to questionnaires, history, and laboratory data are kept confidential. No names appear on information collected. Materials will be labeled with a code number known only to project staff. All data will be de-identified prior to transferring from the MEDVAMC using encrypted drives. Electronic data will be transferred quarterly by study staff, to be placed on an encrypted and password protected drive (Aegis Padlock – USB 3.0, 100% hardware-based encryption) and then uploaded to BCM's RHEL 7.3 server (located at 1 Baylor Plaza, Jones Building, Room 367EB), which is also password-protected and managed by BCM IT. The network path to the data will be IP: 10.16.88.30 and server path /raid5/rcho/VA_R61_DATA. MATLAB and FSL will be used in order to analyze EEG and fMRI data, respectively. Data will be accessed by study staff personnel only through the use of access privileges and passwords. Once data is transferred to BCM, the two datasets (from MEDVAMC and BCM sites) will be combined to create the final dataset to be held and analyzed at BCM. Research records, including identifiers will be destroyed six years after cutoff (at the end of the fiscal year) after completion of the research project, but may be retained longer if required by other federal regulations or sponsor archive requirement.

During the course of the study, trained research staff supervised directly by the PI will monitor participants. The study coordinator and data analysts will meet weekly with the PIs (and/or appropriate co-investigators), to review data and study issues including data analysis, recruitment, and confidentiality. In the event of an adverse event or breaches in confidentiality, the research staff will immediately communicate to the PI. This information will be communicated immediately to the IRB. If changes to the protocol become necessary to insure continued confidentiality measures, or to ensure the level of risk associated with this study, the IRB will be notified immediately, and these modifications will be addressed for review and approval as quickly as possible. Except for adverse events or modifications, a summary of study progress will be forwarded to the IRB a with the annual renewal application. There is no conflict of interest on the part of any of the key personnel associated with this study. Information about this study can also be found at clinicaltrials.gov.

An Accounting and Disclosure (AOD) will be created and maintained for any disclosure of individually identifiable information (III) outside the VA. The manual spreadsheet will include the date of the disclosure and the name and address of person or agency to which the disclosure was made.

Publication Plan

Final analysis and preparation of manuscripts will occur during months 23-24 of Phases 1 and 2 respectively.