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PROTOCOL COVER PAGE

Protocol Title	Modulating Human Cortical Plasticity with Transcranial Electrical Stimulation
Principal Investigator/Faculty Advisor	Name: Kelvin O. Lim
	Department: Psychiatry
	Telephone Number: (612) 273-8700
	Email Address: kolim@umn.edu
Student Investigator	Name: Elias Boroda
	Current Academic Status (Student, Fellow, Resident): Graduate Student
	Department: Neuroscience
	Telephone Number: 7634984176
	Institutional Email Address: borod002@umn.edu
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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
		Crossover to new template	n/a

Table of Contents

ABBREVIATIONS/DEFINITIONS

- tDCS – Transcranial Direct Current Stimulation
- EEG – Electroencephalograph
- ERP – Event Related Potential
- SSP – Stimulus Specific Plasticity
- AEP – Auditory Evoked Potential

1.0 Objectives

1.1 Purpose: *Experience dependent plasticity is a fundamental property of the brain. It allows neural systems to adapt in response to environmental input and subserves the vital functions of learning and memory. Deficits in plasticity are also thought play a causal role in the pathophysiology of several psychiatric disorders, specifically schizophrenia (SZ). Treatments that can probe or even enhance plasticity have potential to be of great clinical and research value. Non-invasive neuromodulation via transcranial direct current stimulation (tDCS) is a promising method for modulating neural plasticity. tDCS delivers low-intensity direct current to cortical areas, thereby facilitating or inhibiting neural activity in a polarity specific manner. Due to its low cost and safety, tDCS has been employed in a wide variety of studies, but much remains unknown regarding its mechanism of action in humans. Experiments carried out in animal and tissue models indicate that tDCS modulates synaptic plasticity mechanisms of long term potentiation and depression (LTP/D), however, these findings have never been translated to human subjects, limiting the practical utility of the research. Recently developed electroencephalographic (EEG) based measures now allow the interrogation of synaptic plasticity non-invasively in humans, making it possible to explore the effects of tDCS on human brain plasticity.*

Specific Aims:
1. Evaluate the effects of Anodal tDCS vs. Sham in enhancing the induction of plasticity in the auditory cortex in healthy participants.

Hypothesis: Anodal tDCS will enhance the induction of LTP (as measured by potentiation of AEP's) compared to Sham.

2.0 Background

2.1 Significance of Research Question/Purpose: *Experience dependent plasticity is generally defined as the ability of a nervous system to dynamically shift functional or structural states in response to extrinsic and intrinsic factors. Research over the past 50 years demonstrates that experience dependent plasticity is a fundamental property of the brain and is critical for everyday functioning. It allows us to learn and recall patterns, predict and obtain reward, and guides response selection for adaptive behavior (Cooke and Bliss, 2006; Ganguly and Poo, 2013). Given its fundamental role in brain dynamics, maladaptive experience dependent plasticity can lead to debilitating conditions. Disrupted synaptic plasticity is thought to play a significant role in the pathophysiology of several severe psychiatric disorders, including schizophrenia (SZ), bipolar disorder and major depressive disorder (Elvsåshagen et al., 2012; Normann et al., 2007; Stephan et al., 2006). The contribution of disrupted plasticity is most clearly*

implicated in SZ, a serious neuropsychiatric illness that impacts 1% of the population and presents with a host of positive, negative and cognitive symptoms. Therefore, treatments that can assess or even enhance plasticity have the potential to be of great clinical value.

Non-invasive neuromodulation via transcranial direct current stimulation (tDCS) is a promising method for modulating plasticity. Due to its low cost, tolerability and simplicity, the use of tDCS in both research and clinical settings has grown substantially. The beneficial effects of tDCS have been reported on a wide range of faculties, including learning and various cognitive abilities (Hill et al., 2016). Clinically, it has been used to treat a plethora of symptoms, from cognitive deficits to psychotic symptoms (Kekic et al., 2016). Despite the positive effects however, significant issues, such as moderate effect sizes and a high degree of variability in outcomes, limit the clinical potential of tDCS. One factor that contributes to these issues is the paucity of research that has investigated the mechanism of action of tDCS in humans. The vast majority of studies looking at this question have been conducted in animal or tissue models. Findings from these studies clearly demonstrate that tDCS effects are mediated by modulating plasticity mechanisms. However, due to the invasive techniques used to gather this data, recapitulating these findings in human subjects has not been possible. Techniques that can parallel the experimental procedures used in animal models are necessary to bridge the translational gap. A recently developed paradigm, termed stimulus specific plasticity (SSP), is a close parallel to the high frequency electrical stimulation protocols used in studies that investigated the impacts of tDCS on plasticity in animals and tissue slices. SSP utilizes sensory stimuli to evoke neural responses that can be recorded via the electroencephalogram (EEG), and has been shown to be functionally equivalent to the plasticity inducing paradigms used in model systems. This project has a strong translational application due to the paradigms that will be utilized. We will be translating much of the work that has been conducted in animal and tissue models which shows the modulatory effect of tDCS on synaptic plasticity. Translation of these findings to humans is necessary to better understand the mechanisms of tDCS and also to validate the animal models themselves. In addition, tracking tDCS effects with SSP allows the probing of neural plasticity in the sensory cortices, something that has generally been limited to the motor cortex in the past (via Transcranial Magnetic Stimulation). Given the fact that sensory processing is disrupted in psychiatric illnesses such as SZ, monitoring plasticity in these regions may also has a strong clinical significance. Finally, SSP allows the non-invasive assessment of the efficacy of treatments that are aimed at enhancing brain plasticity. In that sense, this project will serve as a proof of concept for studies that seek to assess effectiveness of tDCS intervention.

TDCS Modulates Synaptic Plasticity: tDCS is a neuromodulatory technique in which low-intensity direct current is conducted to the brain through scalp electrodes. Most commonly, two electrodes are utilized, an anode and a cathode. Anodal stimulation produces a shift in excitability that depolarizes neurons, while cathodal stimulation has opposite effects. These assumptions are only generalizations however, as it has been demonstrated that neuronal activity and morphology play a greater role in directionality of effects than previously thought (Kronberg et al., 2016). Though current spread from tDCS is rather diffuse, a degree of focality can be achieved as current density is highest directly underneath the electrodes (Bikson et al., 2012; Datta et al., 2009). Though the cellular mechanisms of tDCS are still under investigation, it is known that stimulation changes resting membrane potential (in a polarity specific manner), and modulates synaptic plasticity mechanisms of long term potentiation and depression (LTP/D). LTP refers to the lasting functional (or structural) enhancement of synaptic connections that occurs through coincident pre and postsynaptic activity. This concept, first postulated by Donald Hebb (Hebb, 1949), has several properties that make it an attractive candidate for serving as the substrate for learning and memory (Rioult-Pedotti et al., 2000). First, LTP is persistent, lasting from several minutes to months (Abraham et al., 2002). Second, it is input specific, in that the potentiation is restricted to active synapses only. Third, it is associative and cooperative, meaning that weakly stimulated synapses can still be potentiated if associated in time with other inputs that depolarize the postsynaptic cell (Kitajima and Hara, 1991). Lastly, LTP relies on the coincidence detecting mechanism provided by the NMDAR and is thus dependent on NMDAR activation (Rioult-Pedotti et al., 2000). Investigations of the effects of direct current stimulation on LTP/D have primarily been carried out in excised tissue samples from the hippocampus or the motor cortex of mice (Fritsch et al., 2010; Kronberg et al., 2016). In these studies, LTP is induced by applying a high frequency train of electrical impulses (HFS) to an afferent pathway. This causes the coincident activation of pre and postsynaptic cells, leading to enhancement of synaptic strength as measured by the slope of excitatory postsynaptic potentials (ESPS). Multiple studies have shown that when applied during this protocol, direct current stimulation acts to modulate the potentiation of EPSPs. Anodal stimulation was found to enhance potentiation (Fritsch et al., 2010; Kronberg et al., 2016; Ranieri et al., 2012), while cathodal stimulation had varying effects depending on location of the recording electrode (Kronberg et al., 2016). It is important to note that direct current stimulation provides only a subthreshold change in membrane potential and does not on its own induce LTP. Thus tDCS relies on concurrent synaptic activity to enhance plasticity (Fritsch et al., 2010). The facilitation of LTP via tDCS has also been demonstrated in vivo in animal models. Here, learning of a motor task was

used to induce LTP in behaving mice who were treated with anodal or sham (placebo) stimulation over the motor cortex (Fritsch et al., 2010). Immediately after learning the task, LTP was assayed by eliciting EPSPs from the layers II/III of the motor cortex. Mice who had received tDCS while learning the task displayed enhanced elevation of EPSPs compared to sham stimulated mice. In addition, the rate of learning on the motor task was significantly higher in the active stimulation group. These works demonstrate that tDCS effects on the brain are emergent from a modulation of plasticity mechanisms.

Very little work has been done that translates the findings from the aforementioned studies to human subjects. The only studies that have probed the effects of tDCS on plasticity in humans have done so in the motor cortex. These studies use Transcranial Magnetic Stimulation (TMS) triggered motor evoked potentials (MEP) as measures of synaptic potentiation. This method of probing plasticity is lacking in several regards. First, MEP's are not a direct measure of brain activity. Second, due to reliance on MEP's, these investigations are confined to the motor cortex, restricting the scope and the applicability of findings. Finally, the paradigm does not induce LTP and is not a close parallel to the HFS protocols used in animal/tissue models, thus limiting translational relevance.

SSP is a Non-Invasive Measure of Synaptic Plasticity: Recently developed techniques utilizing the EEG now enable the non-invasive interrogation of synaptic plasticity in the human cortex. As demonstrated first by Clapp et al., (2005), and since then by others (Teyler et al., 2005; Zaehle et al., 2007), it is possible to induce LTP in the human sensory cortices by the rapid presentation of sensory stimuli. It has been shown that a rapidly presented checkerboard pattern (a photic tetanus) can induce long lasting changes in evoked potentials (Teyler et al., 2005), spectral features (Clapp et al., 2006a), and hemodynamic response (Clapp et al., 2005a) in the visual cortex. Similar findings have been reported in the auditory cortex with rapid presentation of auditory tones (Clapp et al., 2005b). Here, the N100 component of the auditory evoked potential (AEP) was potentiated post auditory tetanus. The N100 component is a negative peak that emerges just anterior of the Cz electrode and is thought to emanate from the bilateral superior temporal gyri (Ford et al., 2016; Zaehle et al., 2007). The potentiation of the AEP post tetanus was independent of arousal state and persisted for over an hour without decrease. Studies of SSP in rats demonstrate that the potentiation effect is long lasting, NMDAR dependent and input specific, supporting the theory that SSP is indeed inducing LTP (Clapp et al., 2006b). This paradigm is thus a close parallel to the high frequency electrical stimulation that is used to induce LTP in animal and tissue models. These properties make SSP an ideal translational tool for

recapitulating the work done in models regarding the effects of tDCS on neural plasticity. To date no one has used SSP to analyze tDCS effects.

The fact that SSP allows the interrogation of plasticity in the sensory cortices is relevant from a clinical perspective as well. Several psychiatric disorders present with disrupted functioning of the sensory areas. This is especially notable in SZ, where disruptions of synaptic plasticity in the auditory cortex result in deficits of auditory perception and can lead to hallucinations (Gaebler et al., 2015; Sweet et al., 2009). A pertinent study by Mears and Spencer (2012) utilized the auditory SSP paradigm to assay LTP induction in SZ patients, finding a lack of potentiation in the N100 component (compared to healthy controls). A more recent paper utilized visual SSP to evaluate the effectiveness of D-cycloserine (an agonist of the NMDAR) on enhancing plasticity (Forsyth et al., 2015). Together these studies demonstrate that SSP can be used to both assay the integrity of the brain to support LTP, and as a tool to gauge the efficacy of treatments that are aimed at enhancing plasticity. Demonstrating the effects of tDCS on plasticity measures in healthy humans, is a necessary step prior to carrying this study out in a clinical population.

2.2 Preliminary Data: *N/A*

2.3 Existing Literature: *See Section 2.1*

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome: *Change in amplitude of AEP as recorded by the EEG. Change in AEP is a proxy for brain plasticity.*

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s): *N/A*

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description: *Transcranial Direct Current Stimulation (tDCS) is a noninvasive method of neuromodulation which applies low levels of electrical current to the scalp. TDCS can modulate plasticity and has been used for a variety of clinical and research purposes. We will apply tDCS bilaterally to the auditory cortex.*

4.2 Drug/Device Handling: *We will be using the StarStim8 (Neuroelectrics) device for tDCS and EEG recording. This device has been approved for use in research without an investigational device exemption due to meeting criteria for non- significant risk (NSR). In addition, the device has built in safety mechanisms which allow for the immediate cessation of stimulation should the subject become uncomfortable or if the impedance of the stimulation electrodes is too high. Stimulating electrodes will be placed over the auditory cortex and return electrodes will be placed over the supraorbital bone. 1 mA of current will be delivered for the duration of*

stimulation. The device will be stored in a locked cabinet in our lab space. Our lab space on the 5th floor of the secure 717 Delaware Research Building. Only trained team members who are on the IRB protocol will have access to the locked cabinet.

4.3 Biosafety: *N/A*

4.4 Stem Cells: *N/A*

5.0 Procedures Involved

5.1 Study Design: *The study will be conducted in a blinded, within-groups design involving two separate study sessions. The two sessions will consist of simultaneous tDCS and EEG recording. Each participant will receive both active and sham tDCS over the course of the two sessions (but not within a single session). Order of stimulation type will be counterbalanced across participants. The two sessions will be spaced at least 24 hours apart. The consent process will be done at the first study session. The primary outcome measure will be the difference in the amplitude of the ERP's (specifically the N100 component) recorded before and after tDCS. This difference is reflective of the capacity of the sensory cortex to support synaptic plasticity.*

5.2 Study Procedures:

- Screening Visit: *The screening process will happen over email or phone (depending on how participant makes contact). Potential participants will be provided with information about the study using an established script and will be asked a series of questions to determine if they meet basic inclusion/exclusion criteria (see below). They will be told about the basic aims of the study, and those interested in participating will be scheduled for the study.*
- Study visits: *Visits will take place at our 717 Delaware Street SE offices, the Ambulatory Research Center (ARC) at the department of Psychiatry, or at the clinical spaces at our St. Louis Park location. At the first study session, the participants will complete the informed consent process. The participant will also be told that this is not a treatment study and no benefits to the participant are expected from the study. After, and if, they complete the process, the participant will fill out the tDCS Side Effect Questionnaire (TSEQ), and the Edinburgh Handedness Inventory. These two brief questionnaires ask about potential side-effects of tDCS and the subject's handedness respectively. After the paperwork has been completed, the participant will undergo EEG and either active or sham tDCS (see embedded figure). The stimulation and the recording will be provided using the StarStim Neurostimulator (Neuroelectrics, Inc.). This device has been approved for use in research in the United*

States without an investigational device exemption due to meeting criteria for non-significant risk. The device utilizes standard Ag/Cl electrodes embedded in an easy to use neoprene cap. A small amount of conductive gel is applied to each electrode before insertion into the head cap. Electrodes will be positioned on the subject's scalp according to the international 10/20 electrode placement system. During EEG recording, all electrodes will be utilized to record brain signal. The session will begin with EEG recording while the participant engages in a visual search task. Immediately after, either a passive Auditory Oddball paradigm or a passive Visual Oddball paradigm (these tasks are described in detail in the instruments section) will begin. They will be seated in front of a monitor as the observe visual stimuli or will be wearing insert headphones through which auditory stimuli will be delivered. After the first Oddball task, simultaneous EEG and tDCS will commence for a period of 10 min. During simultaneous EEG and tDCS, two electrodes will be used to deliver stimulation, while the remaining electrodes continue to record EEG. The two stimulation electrodes will be positioned bilaterally over the auditory cortex (T3/T4). In the anodal group the device will deliver 1mA of current through each stimulating electrode. The current is initiated in a ramp like fashion over a 10 sec period from 0mA to 1mA. Once at 1mA, the current is held constant for the duration of the session. Should the participant not be able to tolerate a current of 1mA due to pain or irritation, the current will be decreased down to a minimum of 0.5mA. If 0.5 mA is still not tolerable, the participant will be removed from the study. The sham procedure involves only 40 sec stimulation at 1mA and then drops to 0mA with 15ms pulses every 550ms. This simulates the tingling sensations that are often associated with active stimulation. 15min into the stimulation session the sensory tetanus will commence. The auditory tetanus involves the presentation of a 1000Hz tone at a rate of 13Hz for a period of approximately 5min. The visual tetanus involves the presentation of the visual stimulus (either a horizontal or vertical grating) at a rate of 9Hz). Sensory tetanus and tDCS will end at the same time. Briefly after tetanus and tDCS, the participants will perform the second oddball task as well as a final visual search task.30 min after the cessation of tDCS, a final oddball task will be conducted. After the completion of the EEG recording, the head cap will be removed and the participant will be given the opportunity to wash their hair (towels and shampoo provided). The two study sessions will be identical, differing only in type of tDCS applied (sham or active).

- Precautions Taken*: tDCS is considered to be a safe brain stimulation technique that rarely result in adverse events. There is currently no evidence of serious side-effects. We will discontinue any participant who experiences sores at the tDCS administration site, headaches that*

impair global functioning, and worsening psychosis. Mild side-effects typically resolve upon discontinuation tDCS. The participant may choose to discontinue stimulation at any time during the session if experiencing discomfort or side effects. No other risks are anticipated. Nonetheless, in order to minimize risks, study staff will be using standards of administration that have been shown to be safe in numerous other studies and across more than 2000 studies (Liebetanz et al., 2009; Nitsche et al., 2007; Poreisz, Boros, Antal, & Paulus, 2007) using tDCS; this includes length of administration, magnitude of the current, size of electrode sponges used, and method of applying stimulation. Any unanticipated problems or adverse events will be reported according the University of Minnesota IRB standard operating procedure. 2. Participants will be informed that they are not required to answer any questions or participate in any activities which make them uncomfortable. 3.The results of this study may be published or presented but the participant's identity and records will not be revealed unless required by Federal Law. A Federal Law allows the U.S. Food and Drug Administration, Office for Human Research Protections, Government Accountability Office and other Federal agencies, the Research and Development Committee, representatives of USAMRMC, Henry M. Jackson Foundation, the University of Health & Biological/Medical Application Form 11 Minnesota Institutional Review Board (IRB), and/or the Institutional Review Board (IRB)/Human Studies Subcommittee of the VA Medical Center to review records. Because of the need for these inspections, absolute confidentiality cannot be guaranteed. However, every effort would be made to minimize these risks by providing the participant with a unique numerical identifier at the beginning of the study in order to protect their actual identification and maintain complete confidentiality.

5.3 Study Duration: *We plan on enrolling participants through May 2019. Data analysis should be completed by December 2019.*

5.4 Individually Identifiable Health Information: *Basic information regarding participants, name, email, phone number, address and DOB will be collected. See the HIPCO form for more details.*

5.5 Use of radiation*:* N/A

5.6 Use of Center for Magnetic Resonance Research*:* N/A

6.0 Data and Specimen Banking

6.1 Storage and Access: *All participants will receive a unique numerical ID which will be used in lieu of identifiable information whenever possible. All source data containing identifiers will be stored in locked cabinets in locked*

rooms. All digital identifiable data will be stored on access-controlled, password-protected databases.

6.2 Data: *Deidentified Neuroimaging data (EEG recordings) will be the only data stored*

7.0 Sharing of Results with Participants

7.1 *Results of the study will not be shared with participants. The findings of the study will be shared via publication or presentation at a conference once all data has been collected/analyzed.*

8.0 Study Population

8.1 Inclusion Criteria: *Participants will be recruited from the University and surrounding community. No vulnerable populations will be recruited for this study. Specific inclusion criteria are listed below:*

- *Between 18-50 years old*
- *Normal hearing ability*
- *No psychiatric medication prescription*
- *No clinically significant head injury or neurological disease*
- *No drug dependence past 6 months or no substance abuse in the past month*
- *Sufficient spoken English to understand study procedures*
- *Ability to give informed consent*

8.2 Exclusion Criteria: *Exclusion criteria are listed below:*

- *History or tDCS or other cortical energy exposure within past 12 months*
- *History of seizures or epilepsy*
- *Cranial metallic plates/screws*
- *Implanted devices*
- *History of craniotomy*
- *History of eczema on scalp*
- *Bipolar disorder or Depression diagnosis*
- *Cornrows or dreadlocked hair*
- *Impaired hearing*

8.3 Screening*: The screening process will happen over email or phone (depending on how participant makes contact). Potential participants will*

be provided with information about the study using an established script and will be asked a series Health & Biological/Medical Application Form 7 of questions to determine if they meet basic inclusion/exclusion criteria. They will be told about the basic aims of the study, and those interested in participating will be scheduled for the study. At the study visit, the participants will first complete the informed consent process

9.0 Vulnerable Populations

9.1 Vulnerable Populations:

- ☐ Children
- ☐ Pregnant women/Fetuses/Neonates
- ☐ Prisoners
- ☐ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders
- ☐ Approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.
- ☐ Disadvantaged in the distribution of social goods and services such as income, housing, or healthcare
- ☐ Serious health condition for which there are no satisfactory standard treatments
- ☐ Fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior)
- ☐ Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research
- ☐ Undervalued or disenfranchised social group
- ☐ Members of the military
- ☐ Non-English speakers
- ☐ Those unable to read (illiterate)
- ☐ Employees of the researcher
- ☐ Students of the researcher
- ☐ None of the above

9.2 Additional Safeguards: N/A

10.0 Local Number of Participants

10.1 Local Number of Participants to be Consented: *Up to 80 participants will be consented for the study. The goal is to have 35 complete the study.*

11.0 Local Recruitment Methods

11.1 Recruitment Process: *Recruitment will be conducted using posted flyers as well as ads posted on Craigslist. Flyers will be posted around campus both outside and inside buildings. Ads will be placed on Craigslist under "part time gigs".*

11.2 Identification of Potential Participants: *Interested participants will get in contact with study staff using email or phone calls. Initial contact will be made primarily by the student investigator. No medical records will be asked for/collected as a part of this study.*

11.3 Recruitment Materials: *Recruitment materials include posted flyers and ads on craigslist.*

11.4 Payment: *We will use the Greenphire ClinCard System to pay our participants. Participants will receive the card with $20 preloaded at the end of the first study session. $20 more will be loaded onto the card at the completion of the second study session. Research experience points may also be awarded*

12.0 Withdrawal of Participants

12.1 Withdrawal Circumstances: *If we cannot collect quality EEG data from the subject due to the following reasons, the participant will be withdrawn from the study*

- *Excessively thick hair*
- *Small earlobe (cannot place earclip electrode)*
- *Excessive movement during EEG*
- *Excessive blinking during EEG*
- *Issues with lack of alertness (falling asleep)*

12.2 Withdrawal Procedures: *In the case that a participant withdraws, the PI will be notified and data collection from that subject will immediately cease. Records will be updated to reflect a withdrawal. No partial withdrawal option is given for this study.*

12.3 Termination Procedures: N/A

13.0 Risks to Participants

13.1 Foreseeable Risks: *There is currently no evidence of serious side-effects associated with tDCS. Criteria for discontinuation that may rarely occur are sores at the tCS administration site, headaches that impair global functioning, and worsening psychosis. Mild side-effects that typically resolve upon discontinuation tDCS include light itching under the electrode at the beginning of administration, headache, fatigue, and nausea.*

13.2 Reproduction Risks: N/A

13.3 Risks to Others: N/A

14.0 Potential Benefits to Participants

14.1 Potential Benefits: *No benefits expected for participating in the study*

15.0 Statistical Considerations

15.1 Data Analysis Plan: *Data analyses will include traditional statistical analyses for within-groups differences in EEG neuroimaging data.*

15.2 Power Analysis: *35 participants in a within-groups design will provide the statistical power (1- β = 0.80) necessary to detect effect sizes greater than d' = 0.450. Based on the large effect sizes (d' > 0.68) reported by Clapp et al. (2005) we expect to be sufficiently powered with the aforementioned* sample size.

15.3 Statistical Analysis: *Data will be analyzed in a 2-way ANOVA with correction for multiple comparisons*

15.4 Data Integrity: *EEG data will be subjected to standard quality control measures (both automated and manual) including measuring and controlling for artefacts.*

16.0 Confidentiality

16.1 Data Security: *Data will be handled by trained research staff members. Paper records will be stored in locked file drawers and electronic data storage will meet University security requirements (password protection, encryption, controlled access, audit trails of access, etc.). Protected Health Information will be separated from research data. Research data will be coded and, thus, de-identified. De-identified data will be stored in a local HIPAA-compliant RedCap database or Box Storage managed by the University of Minnesota. Signed consent forms will be scanned into the OnCore system as required by the University. Research information will not be placed into the individual's electronic medical record.*

17.0 Provisions to Monitor the Data to Ensure the Safety of Participants

17.1 Data Integrity Monitoring: *The principal investigator will monitor safety and data quality for this study. They will ensure that adverse events are reported accordingly and that data are generated, documented (recorded), and reported - in compliance with this protocol, with Good Clinical Practice, and any other applicable regulatory requirements. In addition, independent research monitoring will be conducted by the Clinical and Translational Science Institute (CTSI). A CTSI staff member, Lisa Hostetler, will act as the regulatory monitor for this study. Her duties will include*

reviewing regulatory binders and patient files to make sure that the research is being conducted properly

17.2 Data Safety Monitoring. N/A

18.0 Provisions to Protect the Privacy Interests of Participants

18.1 Protecting Privacy: *Participants are free to contact the study team and will not be directly contacted unless they indicate an interest. During screening and consent, participants will be given the option to not participate at any point. Before the start of the first and second study sessions, the participant will again be given an option to discontinue. We will stress that if at any point anything feels uncomfortable, they can let us know and we will quickly resolve the situation.*

18.2 Access to Participants*: No medical records will be assessed*

19.0 Compensation for Research-Related Injury

19.1 Compensation for Research-Related Injury: *In the event that this research study results in an injury, we will provide treatment including first aid, emergency care, and follow-up as needed. Care for injuries would be billed in the ordinary manner and costs would not be covered by the research study itself.*

19.2 Contract Language: N/A

20.0 Consent Process

Note: The process and documentation plan must follow "SOP: Informed Consent Process for Research (HRP-090)" and "SOP: Written Documentation of Consent (HRP-091)."

20.1 Consent Process (when consent will be obtained): *Consent will be obtained in our lab spaces in the 717 Delaware Research Building. Participant and study team member will go through the entirety of the document together, then the participant will be given as much time as needed to review the document on his/her own. Questions regarding the study/consent form will be encouraged. The study team member may ask the participant if he/she understands the study procedures and may ask to have the participant relay the major items in the consent form. The voluntary nature of the study will be stressed at all times.*

20.2 Waiver or Alteration of Consent Process (when consent will not be obtained): N/A

20.3 Non-English Speaking Participants: *Non-English speaking participants will not be recruited for the study*

20.4 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): *N/A*

20.5 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: N/A

20.6 Adults Unable to Consent: N/A

21.0 Setting

21.1 Research Sites: *Participants will be recruited from around the University campus areas as well as in the greater Twin Cities area via Craigslist postings. Study visits will take place at our 717 Delaware Street SE offices, the Ambulatory Research Center (ARC) at the department of Psychiatry, or at the clinical spaces at our St. Louis Park location.*

21.2 International Research: N/A

22.0 Multi-Site Research N/A

23.0 Resources Available

23.1 Resources Available:

- *Dr. Kelvin Lim has a wealth of experience carrying out tDCS studies and will have direct oversight of this study. He will train and have weekly interactions with the student investigator. The weekly meetings will involve review of data, reporting of any adverse effects and continued training on tDCS and EEG.*
- *We have recruited healthy participants from the University in the past using similar techniques and have has no issues meeting our required sample sizes.*
- *Dr. Lim will be devoting about 15% of his time to this study, Elias Boroda, the student investigator, will devote 65% of his time to the study.*
- *Study visits will take place at our 717 Delaware Street SE offices, the Ambulatory Research Center (ARC) at the department of Psychiatry, or at the clinical spaces at our St. Louis Park location. All 3 of these locations have designated rooms for EEG data collection and are all suited for tDCS studies. These locations provide laundry services for towels (needed for cleanup) as well as technical support for troubleshooting EEG.*
- *Though we do not anticipate any adverse effects requiring medical intervention, we do have licensed medical professionals working on the same floor as all of our 3 locations.*
- *Dr. Lim will ensure that all study team members are trained on the protocol and are appropriately overseen.*

24.0 References

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