Modulation of Motor Cortex Excitability by TMS and tDCS (MAGS1)

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MODULATION OF MOTOR CORTEX EXCITABILITY BY TRANSCRANIAL MAGNETIC STIMULATION AND TRANSCRAINAL DIRECT CURRENT STIMULATION

A pilot and single-site study for modulation of motor cortex excitability by transcranial magnetic stimulation and transcranial direct current stimulation

Funding Mechanism: *Foundation of Hope for Research and Treatment of Mental Illness*

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Co-Investigator:

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LIST OF ABBREVIATIONS

ADM	Abductor digiti minimi
ANOVA	Analysis of Variance
BIS/BAS	Behavioral Inhibition System / Behavioral Approach System
CFR	Code of Federal Regulations
CI	Confidence interval
Co-I	Co-Investigator
CRF	Case Report Form
DC	Direct current
DHHS	Department of Health and Human Services
DMV	Department of Motor Vehicles
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (Version 5)
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EEG	Electroencephalogram
EMG	Electromyography
EOG	Electrooculography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hz	Hertz
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IRI	Interpersonal Reactivity Index
M1	Primary motor cortex
NAMI	National Alliance on Mental Illness
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NRB	Neurosciences Research Building
OCD	Obsessive-Compulsive Disorder
OHRE	Office of Human Research Ethics
OHRP	Office for Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator
PMA	Premarket Approval
SMC	Safety Monitoring Committee
SPI	Serial Peripheral Interface
SOP	Standard Operating Procedure
tACS	Transcranial Alternating Current Stimulation
tDCS	Transcranial Direct Current Stimulation
TEP	TMS-evoked potential
TMS	Transcranial Magnetic Stimulation
UE	Unexpected Event
UNC	University of North Carolina
UNC-CH	University of North Carolina at Chapel Hill

US United States

STUDY SUMMARY

Title	*Modulation of motor cortex excitability by transcranial magnetic stimulation and transcranial direct current stimulation*
Short Title	*TMS*
Protocol Number	*17-0149*
Phase	*Pilot*
Methodology	*Single-site*
Study Duration	*This study is expected to last 2 month.*
Study Center(s)	*This is a single-site study performed at The University of North Carolina at Chapel Hill.*
Objectives (Purpose)	*Purpose of this pilot study is to modulate the motor cortex excitability by transcranial magnetic stimulation and transcranial direct current stimulation. Electromyography will be recorded on right abductor digiti minimi muscle to find the motor threshold and measure motor evoked potentials for each healthy participant. Electroencephalography will be collected on the scalp with a 128-channel net to record TMS-evoked potential.*
Number of Subjects	*18*
Diagnosis and Main Inclusion Criteria	*Eligible participants will be healthy individual without any severe illness and mental disorder.*
Description of Intervention (Procedures/methods)	*Each participant will be seated in a reclining chair and applied non-invasive magnetic and electrical stimulations on the scalp. At baseline, the participant's resting motor threshold (RMT) will be estimated by adjusting the intensity of TMS applied on the left motor cortex to achieve an MEP of about 50uV with 10 TMS pulses at a rate of 0.25Hz. Then a 3-condition, 3-session, 6-sequence randomized crossover experiment will be used to characterize and compare three versions of tDCS stimulation: anode, cathode, sham. Before and after a 10-min tDCS condition is applied, TMS pulses at 120% of RMT intensity will be applied for 5 minutes and TEP and MEP amplitude will be measured.*
Related IRB Applications	*n/a*

1 KEY ROLES

1.1 INDIVIDUALS

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1.2 INSTITUTIONS

The University of North Carolina at Chapel Hill

1.3 OPTIONAL

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1.4 FUNDING SOURCES

Please list below the funding sources for this project:

Sponsor Name	UNC Ramses Number	Sponsor Type	Prime Sponsor Name	Prime Sponsor Type	Sponsor/Grant Number
Foundation of Hope for Research and Treatment of Mental Illness	17-2460	Foundation/Non-Profit	Foundation of Hope for Research and Treatment of Mental Illness	Foundation/Non-Profit	Not applicable

External Funding: This project is externally funded but UNC-CH is not the direct recipient of federal funds.

UNC-CH Funding: This project is not funded through UNC-CH.

Classified: This project is not classified.

2 INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to U.S. and international standards of Good Clinical Practice (FDA Title 21 Part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

2.1 BACKGROUND

Neuronal activity is coded by the frequency of spike firing, which in turn is controlled by the level of the neuronal membrane potential. While more positive potentials lead to increased discharge rates, more negative potentials are associated with reduced firing rates. Transcranial direct current stimulation (tDCS) modulates these processes selectively, depending on the current polarity, duration or strength, and is capable of inducing after-effect excitability changes in the human motor cortex (Nitsche and Paulus, 2000; Baudewig et al., 2001). These features favour the evolution of the tDCS technique as a promising tool in neuroplasticity research as well as a therapeutic instrument in neurological disorders associated with hyper- or hypoexcitable cortex. Previous studies have shown that cerebral excitability was diminished by cathodal stimulation (hyperpolarization) and anodal stimulation leads to an increase in excitability (depolarization) in animal (Bindman et al., 1962; Purpura and McMurtry, 1965). In humans, one study first demonstrated it in invasive epilepsy diagnostics by applying intracranial currents of sufficient strength at intensities of up to 1.5 mA (Dymond et al., 1975). In a non-invasive manner, weak tDCS can alert the cortical excitability using surface electrodes on the scalp (Nitsche and Paulus, 2001, 2000). tDCS differs qualitatively from other brain stimulation techniques because static fields do not yield the rapid depolarization required to produce action potentials in neural membranes (Nitsche et al., 2008). However, tDCS might be considered a neuromodulatory intervention.

Transcranial magnetic stimulation (TMS) is one method used to deliver electrical stimuli through the scalp in humans. In general, single-pulse TMS (including paired-pulse TMS) is used to explore brain functioning, whereas repetitive TMS (rTMS) is used to induce changes in brain activity that can last beyond the stimulation period. Non-invasive TMS of the motor cortex leads to a twitch in the target muscle evoking motor-evoked potential (MEP) on electromyography (EMG). The MEP is usually used to assess the corticospinal tract excitability. On the basis of the computational model (Tofts, 1990), TMS preferentially activates neurons oriented horizontally in a plane that is parallel to both the coil and the brain surface. TMS applied over the motor cortex induces descending volleys in the pyramidal tract projecting on spinal motorneurons, also termed corticospinal tracts. Motorneuron activation in response to corticospinal volleys induced by TMS evokes MEP on EMG recorded by using surface electrodes applied over the muscle belly. In practice, the peak-to-peak amplitude of the MEP and the motor threshold, defined by the minimum TMS intensity required to evoke MEP of at least 50 uV in about 50% of 5 to 10 consecutive trials (Boroojerdi et al., 2001), are both parameters used to estimate the excitability of corticospinal pathways. In addition, combining TMS with electroencephalography (EEG) can capture cortical excitability beyond corticospinal excitability since EEG mainly captures neural activity of the cortical neurons (Farzan et al., 2016). The concurrent combination of TMS with EEG can be a powerful technology for characterizing and modulating brain networks by obtained TMS-evoked potentials (TEPs).

2.2 DOSE RATIONALE

In this study, our primary purpose is to investigate the level at which polarizing currents affect the excitability of the corticospinal system including sham condition. Although it may seem most likely that polarizing currents affect excitability of cortical mechanisms, it is possible that application of the current alters the tonic level of background activity in corticospinal systems and that this produces secondary changes in the excitability of spinal mechanisms that outlast the duration of the stimulus current.

Specifically, we propose an experimental design to modulate motor excitability by different polarity (anode and cathode) and sham of tDCS in human brains. As previous studies showed, tDCS induces persisting excitability changes in the human motor cortex and these plastic excitability changes are selectively controlled by the polarity of tDCS. To reveal the underlying mechanisms of direct current-induced neuroplasticity, we will apply tDCS with 3 different conditions (anode, cathode and sham) and TMS on the motor cortex. Induced cortical- and corticospinal-excitability changes will be assessed by TEPs and MEPs based on individual motor threshold. To reduce a spatial mismatch for targeting primary motor cortex (Diekhoff et al., 2011), in addition, we will collect subjects' individual structural MRI.

2.3 STUDY AIMS/HYPOTHESES

2.3.1 SPECIFIC AIMS

Aim 1. For each tDCS condition, estimate mean changes in TEP and MEP amplitudes induced by tDCS stimulation.

Aim 2. Compare the three tDCS conditions (anode, cathode, sham) in terms of the mean changes in TEP and MEP amplitude.

Aim 3. Obtain statistical estimates of variance components needed for the planning of a future study.

2.3.2 RESEARCH HYPOTHESES

We hypothesize that anodal and cathodal tDCS stimulation increases and decreases TEP and MEP amplitudes compare to sham tDCS condition, respectively. We further hypothesize that TEP and MEP amplitudes are positively correlated.

3 SUBJECT SELECTION AND WITHDRAWAL

A total of 18 participants will be recruited for this study and all data will be collected at UNC-CH. No specific plans have been made to enroll participants from vulnerable populations.

3.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, a participant must meet all of the following criteria:

- Males
- Between the ages of 18 and 35
- Right handed
- Capacity to understand all relevant risks and potential benefits of the study (informed consent)
- Willing to comply with all study procedures and be available for the duration of the study
- Speak and understand English

3.2 EXCLUSION CRITERIA

A potential participant who meets any of the following criteria will be excluded from participation in the study:

- Prior concussion
- Diagnosis of eating disorder (current or within the past 6 months)
- Diagnosis of OCD (lifetime)
- ADHD (currently under treatment)
- Neurological disorders and conditions, including, but not limited to:
    - History of epilepsy
    - Seizures (except childhood febrile seizures and ECT-induced seizures)
    - Dementia
    - History of stroke
    - Parkinson's disease
    - Multiple sclerosis
    - Cerebral aneurysm
    - Brain tumors
- Medical or neurological illness or treatment for a medical disorder that could interfere with study participation (e.g., unstable cardiac disease, HIV/AIDS, malignancy, liver or renal impairment)
- Prior brain surgery
- Any brain devices/implants, including cochlear implants and aneurysm clips
- Traumatic brain injury
- (For females) Pregnancy or breast feeding
- Anything that, in the opinion of the investigator, would place the participant at increased risk or preclude the participant's full compliance with or completion of the study

Justifications for any exclusions based on race, gender, or ethnicity: Non-English speaking individuals are excluded because the ability to accurately and completely communicate study information, answer questions about the study, and obtain consent are necessary.

Previous studies (Becker et al., 1982; Creutzfeldt et al., 1976; Solis-ortiz et al., 1994) demonstrated that there are significant changes in EEG activity with changed hormone levels and spontaneous menstrual cycle. One study revealed that luteal and follicular women showed higher and lower alpha oscillations in resting-state EEG compared to healthy men (Brötzner et al., 2014), respectively. In addition to EEG activity, one study found that modulating cortical excitability by TMS is affected by menstrual cycle. They applied TMS pulses to 13 healthy women (luteal and follicular) and found significant changes (p<0.01) in cortical excitability. This study provides the direct evidence of changes in the excitability of a cortical network with the menstrual cycle.
In theory, one could measure female subjects twice during their early follicular phase (± 28 days). However, practically this approach is very difficult to conduct and has some limitations. First, one would need female subjects that have an exact menstrual cycle of 28 days in order to measure at the same weekday and that the time interval. Such a population is very difficult to find and would need at least a 6 month evaluation period of females that have a very stable menstrual cycle. Second, according to literature, the observed variations in EEG activity might reflect the fluctuating actions of the female hormones estrogen and progesterone (Bäckström, 1976). Thus, we would need to control for plasma female hormone levels to assure that those levels were similar for the three tDCS conditions. Thus, because we aim at investigating modulation of cortical excitability with EEG, we need a study population that shows stable EEG activity and excitability.

Justification for excluding women or women who become pregnant: Pregnant participants will be excluded despite the fact that theoretical risk to mother or fetus is exceedingly small, since no safety data for pregnancy is known to exist for TMS/tDCS studies. We will verify pregnancy status via a urine pregnancy test for all female participants.

3.3 STRATEGIES FOR RECRUITMENT AND RETENTION

3.3.1 RECRUITMENT

We intend to recruit 18 healthy participants in the University of North Carolina at Chapel Hill. Study coordinator will be informed of the inclusion and exclusion criteria and will be asked to discuss the study with their subjects. Study coordinator will identify subjects they believe to be appropriate for this study based on the information we will provide them about the study. Study coordinator will ask subjects whether they are willing to be contacted by the research team regarding participation.

3.3.2 RETENTION

Our retention strategy includes a payment schedule of one time per participant. The participant will receive payment at the stimulation session. The research staff will also give each participant a reminder call or email for the stimulation session. Each research staff member will be easily available for the participants to contact via email or phone.

The inclusion criteria state that each participant must be able to understand all risks and benefits associated with this study. We will be asking each participant to answer questions about the consent form to determine that the study process and the duration of participation are completely understood by all participants. We will aim to have a specific research team member assigned to complete all sessions with the same participant to establish rapport and encourage the participant to continue attending sessions.

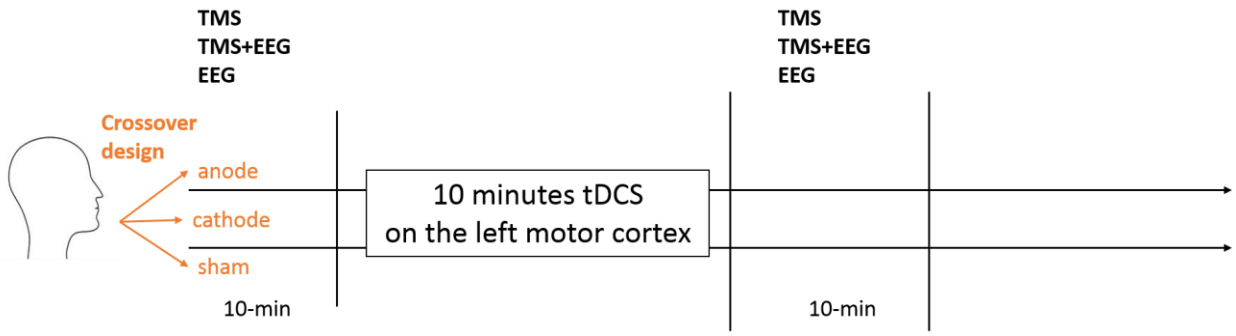
4 BASIC STUDY DESIGN

During each participant's visits, we will screen for eligibility, obtain an estimate of the participant's resting motor threshold (RMT), and conduct a crossover experiment to modulate motor cortex excitability using 3 different conditions of tDCS: anode, cathode, and sham as a control.

- Transcranial magnetic stimulation (TMS)
  To detect current-driven changes of excitability, TEPs on the scalp using EEG net and MEPs of the right ADM will be recorded. Magnetic stimulation with coil will be applied to precisely position the coil over left motor cortex site by a neuronavigation system with individual structural MRI. The TMS coil will be placed tangentially to the scalp with the handle pointing backward and laterally at about 45-degree angle away from the midline, approximately perpendicular to the central sulcus. The stimulation intensity will be adjusted to achieve a baseline MEP of about 50uV with 10 stimuli at a rate of 0.25Hz. The MEPs of the ADM will be recorded using Ag-AgCl electrodes in a belly tendon arrangement. After finding the RMT, TMS intensity will be set to 120% of RMT to evoke motor responses and be applied at a frequency of 0.25 Hz during the following 10-min after tDCS.

- Transcranial direct current stimulation (tDCS)
  Direct current will be applied by a pair of surface rubber electrodes. Position of electrodes will be arranged at left motor cortex and right frontal cortex (forehead above the contralateral orbita), which can lead to significant and reproducible excitability changes. The current will be applied continuously 10-min with an intensity of 2mA according to guideline (Agnew and McCreery, 1987). Constant current flow will be validated by oscilloscope.

Each participant will be seated in a reclining chair and applied non-invasive magnetic and electrical stimulations on the scalp. At baseline, ten TMS pulses at 0.25Hz will be applied on the left motor cortex to find the participant's resting motor threshold (RMT). Then a 3-condition, 3-session (1-day gap), 6-sequence randomized crossover experiment will be used to characterize and compare three versions of tDCS stimulation: anode, cathode, sham. Before and after a 10-min tDCS treatment is applied, TMS pulses at RMT intensity will be applied for 10 minutes and TEP and MEP amplitude will be measured. Resting-state EEG data will be collected. Each session has 1-day gap to reduce outlasting effects.



4.1 TREATMENT ASSIGNMENT PROCEDURES

Each participant will experience all three versions of tDCS (anode, cathode, sham). There are 6 ways to order the three tDCS treatments: ACS, ASC, CAS, CSA, SAC, SCA. By randomization, each participant will be assigned to one of these sequences. Three participants will assigned to each of these 6 sequence groups. (The 6 sequences comprise two Latin squares). Each session has 1-day gap to remove outlasting effects. The randomization schedule will be computed prior to recruitment of subjects and the random assignments will be concealed from the personnel who screen potential participants until the moment that the participant is enrolled and ready for baseline evaluations. To accomplish this, the randomization schedule will be used to create a set of sequentially-numbered opaque sealed envelopes (SNOES).

ACS: Anode → Cathode → Sham (3 participants)
ASC: Anode → Sham → Cathode (3 participants)
CAS: Cathode → Anode → Sham (3 participants)
CSA: Cathode → Sham → Anode (3 participants)
SAC: Sham → Anode → Cathode (3 participants)
SCA: Sham → Cathode → Anode (3 participants)

5 STUDY SCHEDULE

In order to increase data quality, the assessments for an individual participant will be administered by the same researcher. It is important to note that consent, scales, and experiments will all take place in a private room. Any phone calls will take place in a private lab environment as well.

5.1 SCREENING

- Screening via a telephone call

The phone screening allows researchers to screen out participants based on self-report responses and for potential participants to become familiar with the study schedule, including procedures. During the telephone screening, researchers will provide a brief background about TMS, tDCS, and EEG. The timeline will be explained to the participants and the participant will be informed of compensation, both amount and payment schedule. The participant will be asked if they have any questions. Once all questions have been answered, the participant will be asked if he/she is still interested in participating in the study. If yes, the researcher will ask if the participant will provide verbal consent to begin the initial phone screening which will determine eligibility for the stimulation session. *A telephone script, which includes the screening questions, is provided in Appendix E.* If the participant meets initial criteria with these two assessments, the stimulation session will be scheduled and a reminder call or email will be given at least 24 hours before the stimulation session.

5.2 STIMULATION

- Documentation

At the stimulation session, participants will be guided through the consent form. To ensure that all aspects of the research are understood, participants may be asked a series of questions about the research they are about to take part in (*Appendix C*). Once it is clear that the participant understands the consent form they may sign the form.

- Stimulations: TMS and tDCS

MagPro X100 and XCSITE 100 will be used for the magnetic stimulation and direct current stimulation, respectively. All magnetic and direct current stimulations will follow the guidelines (Rossini et al., 2015) and participants will perform the experiment consisting of 3 different conditions for tDCS.

6 STUDY PROCEDURES/EVALUATIONS

6.1 SELF-REPORT MEASURES

Study coordinator will consider using a standard questionnaire to screen TMS/tDCS candidates. The following questions represent the basic information required. Additional information may change according to particular demands. Consensus has been reached for this questionnaire.

1. Did you ever have a concussion?
2. Do you have or have you ever had anorexia?
3. Do you have or have you ever had OCD?
4. Do you have or have you ever had ADHD?
5. Have you ever had a fainting spell or syncope? If yes, please describe in which occasion(s)
6. Have you ever had severe (i.e., followed by loss of consciousness) head trauma?
7. Do you have any hearing problems or ringing in your ears?
8. Are you pregnant or is there any chance that you might be?
9. Do you have metal in the brain/skull (except titanium)? (e.g.,splinters, fragments, clips, etc.)
10. Do you have cochlear implants?
11. Do you have an implanted neurostimulator? (e.g., DBS, epidural/subdural, VNS)
12. Do you have a cardiac pacemaker or intracardiac lines or metal in your body?
13. Do you have a medication infusion device?
14. Are you taking any medications? (Please list)
15. Did you ever have a surgical procedures to your spinal cord?
16. Do you have any disorder related to spinal cord or ventricle?
17. Did you ever undergo TMS in the past?

Affirmative answers to one or more of questions 1–17 do not represent absolute contraindications to TMS, but the risk/benefit ratio should be carefully balanced by study coordinator.

6.2 SPECIAL ASSAYS OR PROCEDURES

6.3.1 MOTOR EVOKED POTENTIAL USING EMG

We will use resting motor threshold (RMT) to evoke motor evoked potential. RMT is determined while the target test muscle is at rest. Complete relaxation can be controlled by checking the absence of EMG at high-gain amplification either visually or by acoustic feedback or both. MEP responses to individual, successive stimuli when elicited in active muscles using threshold intensities may fluctuate in amplitude from 0 to about 1 mV, with a median value around 0.2 mV. EMG will be attached on right ADM using Geodesic 400 system (EGI Inc., Eugene, OR, USA).

6.3.2 TMS-EVOKED POTENTIALS USING EEG

We will collect TMS-evoked potentials (TEPs) using a high-density EEG net elicited by TMS pulses. By recording TEPs on the scalp, we can investigate cortical excitability according to 3 different tDCS conditions. EEG will be collected using Geodesic 400 system (EGI Inc., Eugene, OR, USA).

7 STUDY INVESTIGATIONAL PRODUCT

- Transcranial magnetic stimulation (TMS)

We will use the MagPro X100 system (MagVenture Inc., Alpharetta, Georgia, USA) for magnetic stimulation. The MagPro X100 is an advanced, high performance magnetic stimulator designed primarily for research purposes. It is a high quality tool for researchers with a large choice of stimulating parameters and has stimulation rates up to 100 pps at high intensities and the possibility to combine waveforms and pulse modes.

The simulator has several features:

1. 3 waveforms: Biphasic, Biphasic Burst and Monophasic.
2. Selectable current direction.
3. Stimulation rates up to 100 pulses per second.
4. Easily connects to external equipment via programmable input/output triggers.
4. System operation control via a built-in computer, eliminating the need for an external computer to set up and control the timing of stimulus sequences.
5. Controllable from an external device.

- tDCS

We will be using the XCSITE100 stimulator designed in the Frohlich Lab for investigational purposes. The device is not implanted and has not been designed for or being used to support or sustain human life. This device does not have a potential for serious risk to the health, safety, or welfare of the participant. There has never been an instance of serious side-effect reported due to the use of transcranial brain stimulation. Previous studies in the Frohlich lab that used comparable devices (i.e., the commercial, CE-certified Neuroconn Plus stimulator) have always been classified as “non-significant risk” by the full UNC IRB. The Neuroconn Plus stimulator and the XCSITE100 stimulator are electrically equivalent and provide the same stimulation.

The XSCITE100 is the first non-invasive brain stimulator designed for research purposes to provide an active sham for tACS and record the stimulation output for later validation. This stimulator may apply either tDCS or tACS for up to 40 minutes (2400 seconds) with appropriate current ramp-up at the beginning of stimulation and ramp-down at the end of stimulation. Both tDCS and tACS may be applied for currents between 100 µA and 2 mA (peak-to-peak for tACS).

The stimulator has two main components:

- Android tablet with user interface application (i.e., App)
- Stimulator with:
    - Microprocessor
    - Function generator chip
    - Voltage controlled current source
    - Safety circuitry

To ensure appropriate blinding for each stimulation session, there are designated unblinded individuals to ensure the appropriate stimulation parameters are applied to each participant. These individuals will not interact with participants and will only be involved with the creation of a study file and validation of stimulation waveform.

7.1 SAFETY FEATURES

- TMS

In the USA federal law regulates the sale of Medical Devices through the US Food and Drug Administration (FDA). This is done to ensure safety and effectiveness. Devices which are permitted to be marketed for their intended use must either have a 510(k) or PMA clearance. The use of devices for other than their FDA cleared intended use is considered as investigational. Such use is only permitted if the Investigational Device Exemption (IDE) guidelines have been followed. All investigational devices must be labeled in accordance with the labeling provisions of the IDE regulation (§ 812.5) and must bear a label with this statement:

"CAUTION Investigational Device. Limited by Federal (or United States) law to investigational use."

- tDCS

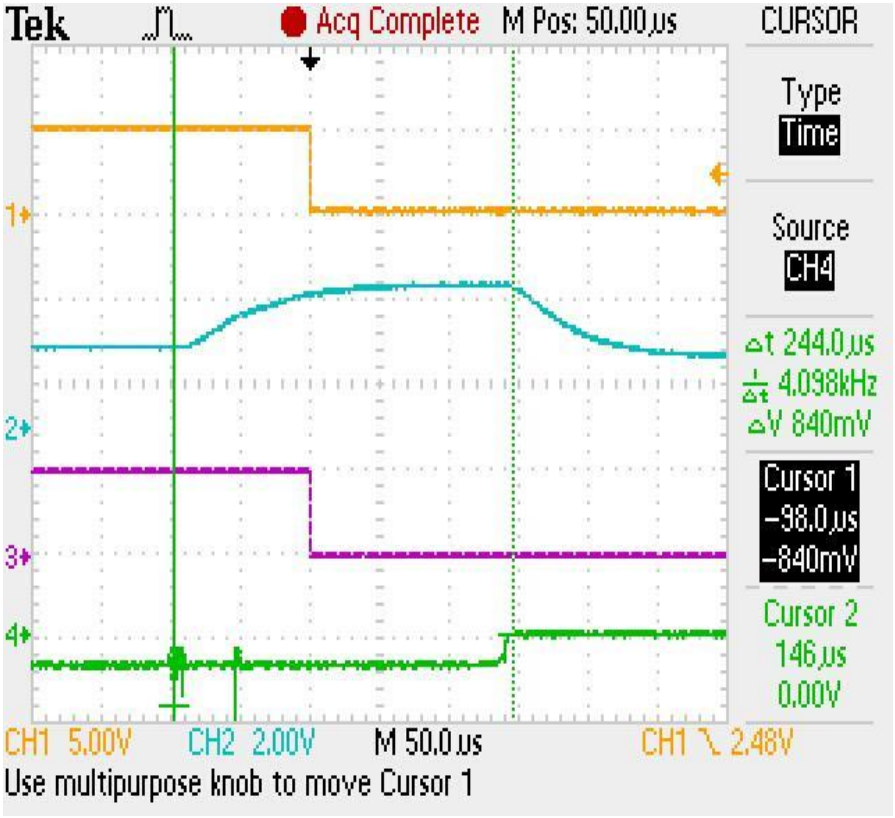
Current Sensor Circuit. A 33.2 Ω sense resistor is placed in series with the stimulation electrodes on the high side. Since high-side current sensing is used, any short circuit of the electrode terminals to ground will be detected. The stimulation current flows through this resistor and creates a voltage. The voltage across this resistor is sensed and amplified by the AD628 difference amplifier. The gain of the difference amplifier is set to 9.9039. The current sensor voltage is then shifted before it is read by the microprocessor and the hardware current safety feature.

Voltage Sensor Circuit. The differential voltage across the electrodes is measured so that the impedance can be calculated. The voltage is measured by buffering the positive electrode and negative electrode each with a unity gain op-amp circuit. The voltage output is then shifted before it is read by the microprocessor using the same level shifting circuit described in the current sensor section.

The device is equipped with 4 different stages of safety precautions, all of which protect the participant from high currents. The stages are as follows:

1. AUTOMATIC SOFTWARE CURRENT CUTOFF. The output of the current sensor described above is read by a microprocessor, which compares the reading to a value of ±3 mA peak. If the current exceeds these limits, stimulation is stopped, a relay in series with the electrode is opened, and the power supply used for stimulation is turned off. The user is then given the option to investigate the issue , and cancel or resume the test. Since high-side current sensing is used (described above), any short circuit of the electrode terminals to ground will be detected.
2. AUTOMATIC HARDWARE CURRENT CUTOFF. The output of the current sensor is fed into a pair of comparators which detect if the current exceeds ±4.5 mA. If so, the fault is latched such that the relay in series with the electrodes is opened. Additionally, the microprocessor is notified of this instance through an interrupt. Upon this interrupt, the microprocessor immediately stops stimulation and the power supply used for stimulation is turned off.

Figure 1. Example of a successful hardware cutoff function



Yellow: Relay control line

Green: Current through electrode (goes from negative current to zero)

Blue: Current sensor output (has lowpass filter)

3. PERMANENT HARDWARE CURRENT CUTOFF. A 5 mA fast-acting fuse is in series with the electrode connector. If the above two over-current detection methods fail, the fuse will below, and the stimulator will no longer be electronically connected to the device.
4. POWER SUPPLY FUSE. Finally, if for no other reason the entire device draws too much current, the main power supply fuse is blown. This fuse is sized with a cutoff of 200% of steady-state operating current.

7.2 PREPARATION AND ADMINISTRATION OF STUDY INVESTIGATIONAL PRODUCT

After participants have completed the questionnaire, they will be comfortably seated. The study coordinator and/or the research assistant will be thoroughly trained and have trainings documented on the transcranial stimulation device and will be present during all stimulation sessions. To monitor side effects of stimulation, a questionnaire will be administered after each stimulation.

7.3 ASSESSMENT OF PARTICIPANT COMPLIANCE WITH STUDY INVESTIGATIONAL PRODUCT

Compliance for this study includes making stimulation session.

8 POTENTIAL RISKS AND BENEFITS

8.1 BENEFITS TO SUBJECTS AND SOCIETY

There is no benefit to subject.

8.2 POTENTIAL RISKS

8.2.1 PSYCHOLOGICAL

Risk of Embarrassment: Self-report questionnaire contains questions regarding personal information. This risk is necessary in order to assess symptomology and associated psychopathology. Participants will be assured upon intake that only study personnel will see any answers.

Risk of Confidentiality Breach. To avoid breaches in confidentiality, study documents that contain personal information, including the informed consent, and the document that links study ID numbers to personal identifying information are kept in locked filing cabinets in locked rooms, separate from any source documents containing participating dummy identifiers. All data is stored in locked cabinets inside locked offices; electronic data will be stored only on password-protected computers, and data encryption methods will be used during communication between investigators. Only study personnel will have access to these data. All study staff participate in annual human participating training that includes education about responsibilities to minimize the risk of confidentiality breach. In the unlikely event of a breach of confidentiality, people might discover that an individual was involved in this research study and some people might not agree with the principle of participating in research or of changing natural brain activity.

8.2.1 PHYSICAL

Risk of Injury and Discomfort: Transcranial direct current stimulation has been used without any reports of serious side-effects for more than a decade and transcranial magnetic stimulation has been cleared for use in the USA by the FDA. These stimulations made has nothing to do with electroconvulsive therapy that applies many orders of magnitude higher stimulation current. Rather, transcranial direct current stimulation is so weak that it does not cause super-threshold activation of neurons. Some participants report a transient mild tingling, burning, or itching underneath the electrodes and headache, but no other side effects have been noted. Importantly, it remains unclear if these mild side-effects were caused by the transcranial brain stimulation. In order to monitor these side-effects, we will be administering side effects stimulation questionnaire after each stimulation session to determine whether these effects were experienced. Research personnel present during these sessions will also check in with the participant periodically during the stimulation to see whether they are comfortable. If any side-effect occurs (rated by the participant as stronger than “moderate”) or the participant is experiencing severe discomfort, the stimulation will be immediately stopped.

8.3 REFERRALS FOR MEDICAL FOLLOW-UP OR PSYCHOLOGICAL COUNSELING

There is a purely theoretical likelihood that stimulation of neuronal circuits can lead to epileptic discharge. To minimize this occurrence, we screen and exclude subjects with personal history of neurological conditions from the study. If abnormalities or a seizure is witnessed during the course of the study, a referral will be made to the UNC Department of Neurology for follow-up. In the theoretical event that a seizure is witnessed that involves the loss of consciousness, the subjects will be told not to operate a motor vehicle until cleared by the DMV.

To ensure participant comfort, a study coordinator or research assistant will periodically check in with the participant about any side-effects he/she may be experiencing during each stimulation.

9 DATA AND SAFETY MONITORING

9.1 FROHLICH LAB MONITORING PLAN

Side effects will be monitored by study coordinator and research assistant on this project. If it seems there are more side effects than expected, an independent review board will be implemented to monitor the situation.

9.2 SAFETY OVERSIGHT BY THE DSMB

A data safety monitoring board will not be used for this study.

9.3 EARLY WITHDRAWAL OF PARTICIPANTS

9.3.1 REASONS FOR WITHDRAWAL

A study participant will be discontinued from further participation if:

- The participant meets any exclusion criteria (either newly developed or not previously recognized).
- Anything that, in the opinion of the investigator, would place the participant at increased risk or preclude the participant's full compliance with or completion of the study.

Participants are free to withdraw from participation in the study at any time upon request.

9.3.2 DATA COLLECTION FOR WITHDRAWN PARTICIPANTS

We will collect safety data on any participant discontinued because of side effect. In any case, every effort will be made to undertake protocol-specific follow-up procedures. If voluntary withdrawal occurs, the participant will be asked to continue scheduled evaluations and complete an end-of-study evaluation. In the case of an early withdrawal, the researcher will make a note to file indicating this.

9.4 TERMINATION OF STUDY

If a seizure occurs at the time of a study visit, a temporary hold will be placed over the study and further investigation will ensue. This could lead to stopping the study prematurely or continuing on with further safety measures in place. If two seizures are witnessed during the study visit, the entire study will be stopped prematurely. These individuals would be referred for further medical attention. It is very unlikely that a seizure will occur.

The study will also be stopped (at least temporarily) if studies provide evidence that transcranial current/magnetic stimulation caused brain damage or other harmful effects on subjects, either short-term or long-term

The IRB will also be informed promptly and provided the reason(s) for the termination of suspension of by the investigator, as specified by the applicable regulatory requirement(s).

10 SAFETY & REPORTING

It is important to assess safety over the course of this study. This section describes in detail how safety is assessed, reporting of side effects and unanticipated problems. This section is a reference for internal use.

10.1 SAFETY PARAMETERS

STIMULATION SIDE EFFECTS. The side effects listed are headache, neck pain, scalp pain, tingling, itching, ringing/buzzing noise, burning sensation, local redness, sleepiness, trouble concentrating, improved mood, worsening of mood, dizziness, flickering lights, and other (specify). Participants are also asked to rate on a 5 point likert scale how related they believe the side effects to be to stimulation (1 = no relation, 2 = remote, 3 = possible, 4 = probable, 5 = definite).

10.2 METHODS AND TIMING FOR ASSESSING, RECORDING, AND ANALYZING SAFETY PARAMETERS

10.2.1 UNANTICIPATED PROBLEMS

Unexpected Events (UE) will be recorded) and will include information such as the date of the event, when the study team was informed of this event, details of the event, when the IRB was notified. The IRB will be notified of each UE that may occur during the study.

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (in the guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If an UE occurs the IRB will be notified and the study will be adjusted as needed to protect the health and safety of the participants. Depending on the nature of the UE, the research protocol, inclusion/exclusion criteria, and informed consent will be changed to reflect the possibility of this event reoccurring. During this time, no new participants will be recruited and the research procedures for currently enrolled participants will be stopped. Each UE will be recorded and reported throughout the study.

11 STATISTICAL PLAN

The statistician for this study is Sangtae Ahn.

11.1 STATISTICAL ANALYSIS STRATEGIES

To help ensure reproducible results, these a priori plans specify the planned analyses for each specific aim along with guidelines for sensitivity analyses performed to assess the robustness of the major results to reasonable perturbations of the assumptions, choices, and methods used. The plans also include 1) secondary analyses as an aid for understanding and interpreting the main analysis results, 2) a role for exploratory analyses for hypothesis generation, and (3) necessary descriptive graphical and tabular methods used to visualize the data, examine relationships among variables, and characterize the participants.

Immediately before and after a 10-min tDCS treatment is applied, TMS pulses at 120% of RMT intensity will be applied for 10 minutes at a frequency of 0.25Hz. For each of those 75 TMS pulses, the MEP amplitude will be measured by EMG in the ADM muscle. Thus, we will have 75 MEP amplitudes before and after each of the 3 tDCS conditions is applied. (In total, each subject contributes 450 MEP amplitudes.) For each set of 75 amplitudes, we will compute the average amplitude. The change in average amplitude (ΔA_{ij}) will be computed as the post-tDCS average minus the pre-tDCS average: $\Delta A_{ij^*} = A_{ij^*}(post) - A_{ij^*}(pre)$ for the i^{th} subject and the j^{th} tDCS condition. The primary analysis will focus on these changes in average amplitude and will rely on a linear mixed-effects model which assumes a compound-symmetry covariance matrix; in other words, a repeated-measures ANOVA model. The dependent variable will be the change in average amplitude (ΔA_{ij^*}) and the explanatory variables will be tDSC treatment condition, treatment period, sequence group (v), and indicator variables representing carryover effects (λ).

Entry is the expected value of ΔA_{ij^*} in the target population	Period 1	Period 2	Period 3
Sequence ACS	$\mu_A + v_1 + p_1$	$\mu_C + v_1 + p_2 + \lambda_A$	$\mu_S + v_1 + p_3 + \lambda_C$
Sequence ASC	$\mu_A + v_2 + p_1$	$\mu_S + v_2 + p_2 + \lambda_A$	$\mu_C + v_2 + p_3 + \lambda_S$
Sequence CAS	$\mu_C + v_3 + p_1$	$\mu_A + v_3 + p_2 + \lambda_C$	$\mu_S + v_3 + p_3 + \lambda_A$
Sequence CSA	$\mu_C + v_4 + p_1$	$\mu_S + v_4 + p_2 + \lambda_C$	$\mu_A + v_4 + p_3 + \lambda_S$
Sequence SAC	$\mu_S + v_5 + p_1$	$\mu_A + v_5 + p_2 + \lambda_S$	$\mu_C + v_5 + p_3 + \lambda_A$
Sequence SCA	$\mu_S + v_6 + p_1$	$\mu_C + v_6 + p_2 + \lambda_S$	$\mu_A + v_6 + p_3 + \lambda_C$

Note: We define $v_6 = (-1) * (v_1 + v_2 + v_3 + v_4 + v_5)$ and $p_3 = (-1) * (p_1 + p_2)$

The fitted model will be used to tabulate statistical estimates (all with 95% confidence intervals) of the parameters of interest: variance components, intra-class correlations, direct effects of tDCS (μ), period effects (p), sequence-group effects (v), and first-order carryover effects of tDCS (λ). We will assume that there are no differential second-order carryover effects. The fitted model will also be used to test the main hypothesis, H_o: "$(\mu_A - \mu_S) = 0 = (\mu_A - \mu_S)$", using an F-test of size α = 0.05. If (and only if) this null hypothesis is rejected, then (and only then) we will test the two component sub-hypotheses using F-tests of size α=0.05: H_{oA} (μ_A-μ_S)=0", H_{oC} "$(\mu_C - \mu_S) = 0$".

We will also perform an equivalence test in which equivalence is defined as a difference of less than $0.1mV$ (i.e., tolerance $T = 0.1mV$. The null hypothesis that the anode and cathode stimulation are not equivalent is $H_o =$ "$|\mu_A\text{-}\mu_C| > T = 0.1mV$". The null hypothesis will be rejected if the 95% confidence interval for $(\mu_A - \mu_C)$ lies entirely within the interval $[-T, T]$.

All hypothesis tests that are observed to be NOT statistically significant will be reported as being inconclusive. Hypothesis tests that are not statistically significant are entirely inconclusive and no conclusions can be drawn from those tests. Every statistical test procedure is (by definition) incapable of establishing that the null hypothesis is true. The word "inconclusive" will be used when reporting a test that was not statistically significant. To avoid over-reliance on p-values, the focus of the analyses will be on point-estimates and interval-estimates of the magnitudes of the population parameters of interest (e.g, effects, correlations, variance components.)

In secondary analyses, time-specific changes in amplitude will be computed as $\Delta A_{ijT} = A_{ijT}(post) - A_{ij^*}(pre) for\ T = 1,2,3, \dots, 75.$ Graphical descriptive statistical methods will be used to visualize and summarize the temporal trajectories of MEP amplitudes.

Sensitivity analyses will be used to evaluate the robustness of the main results to reasonable perturbations of the methods and assumptions used. This set of analyses will examine goodness of fit diagnostics for the linear model, and will include modified versions of the main analyses; e.g., omission of period effects or sequence effects or carryover effects.

For Aim 3, parameter estimates needed for planning a future study will be tabulated along with their 95% confidence intervals. In planning the future study it will be critically important to take into account the levels of uncertainty about the parameter estimates as indicated by the confidence intervals.

11.2 CHOICE OF SAMPLE SIZE

The choice of sample size was based on expert opinion; we conjecture that 18 participants may be sufficient to provide adequate precision for the estimators of variance components and other parameters for which information is needed to plan a future study. As a rough and indirect assessment of the precision afforded by studying a sample of 18 subjects, we considered that an estimate of the proportion of subjects in the target population that would experience a greater increase in MEP amplitude with active tDCS, relative to sham: for an observed estimate of 50%, the 95% confidence interval would span [50% ± 20%]. Or, if 80% was the observed estimate, then the 95% CI would span [80% ± 16%].

11.3 DATA MANAGEMENT

Data will be stored in a password-protected cloud-based data system that does not contain any participant information. Individual records are referred to by dummy identifiers that cannot be traced back to the study participants except with the master code list that is stored separately in a secured location.

12 DATA HANDLING AND RECORD KEEPING

The study coordinator and research assistants are responsible for the accuracy, completeness, legibility, and timeliness of the data reported.

12.1 PHI AND HIPAA

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from the participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

12.2 CONFIDENTIALITY

12.2.1 ACCESS TO SOURCE DOCUMENTS

The research coordinator, research assistants, and PI will have access to all of the source documents collected over the course of the study. The Co-I and medical monitor will have access to files upon request, as they will need access to the locked rooms and filing cabinets in which these documents are located.

Data will stay on a password-protected computer. Subsequently, a copy will be processed on a separate, password-protected desktop computer in the Frohlich Lab (Neuroscience Research Building 4129).

12.2.3 OTHER

Please note that there is no significant risk of deductive disclosure in this study. In addition, none of the groupings or subgroupings used in analysis will be small enough to allow individuals to be identified.

12.3 SOURCE DOCUMENTS

Source data is all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source data include:

PARTNERS HUMAN RESEARCH COMMITTEE (IRB).

- All IRB correspondences are documented
- The study staff is IRB approved prior to performing any study procedures
- All versions of the IRB protocols and informed consent forms are on file

INFORMED CONSENT.

- Ensure that participant identification is not recorded on the ICF (i.e., no participant ID)
- There is documentation that the participant is given a copy of the consent form
- The participant and study representative signed and dated the consent form for him/herself
- The participant initialed and dated all appropriate pages on the informed consent form
- Note to file (Appendix D) made for any informed consent deviations
- Ensure a valid (current version date) copy of the consent form was used

PROTOCOL DEVIATIONS.

- Any and all protocol deviations (exceptions and violations) are documented in the participant folder and reported to the IRB as required

OTHER SOURCE DOCUMENTS.

- Each participant folder will contain a checklist to ensure that all source documents are administered and collected properly. The checklist will be dated by the researcher for each time an assessment is administered
- Review participant folders to ensure the accuracy, completeness, and legibility of the data.
- Any correction made to the source documents is dated, initialed, and explained. The original entry should not be obscured.
- The protocol-specific source documents are on file.
- Source documents are completed in ink.
- Note to files (Appendix D) are made for missing or incomplete data and to explain any discrepancies or additional comments.

12.4 DATA MANAGEMENT RESPONSIBILITIES

The responsibilities designated to each member of the research team are documented on the Delegation of Authority Form. The study coordinator and research assistants will be responsible for the informed consent process, review for eligibility, questionnaire administration, data entry, device administration, EEG administration, and CRF entries. The study coordinator will be responsible for documentation and reporting, while the PI will be responsible for review of the documentation forms, and overview of the research staff.

12.5 DATA CAPTURE METHODS (REDCAP)

All data will be entered into a data capture system provided by REDCap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

All assessments completed by the participant at home will be completed via REDCap as well, ensuring participant security and confidentiality.

12.6 PROTOCOL DEVIATIONS

All deviations from the protocol will be addressed in study participant source documents. The researcher will complete a Protocol Deviation Log using the participant code as the identifier. This form will collect information such as the date the deviation occurred, details of what the deviation consisted of, any corrective and preventative actions that were taken as a result of the deviation, and the date that the PI and IRB were notified. The PI will

review the information and initial once approved. A completed copy of the Protocol Deviation Form will be maintained in the regulatory file, as well as in the participant's source document. Protocol deviations will be sent to the IRB per their guidelines. The site PI/study staff will be responsible for knowing and adhering to their IRB requirements.

12.7 RECORD RETENTION

According to the University of North Carolina at Chapel Hill's Archives and Record Management Services schedule for General Records Retention and Disposition Schedule 6.10, records will be kept for 5 years after the completion of the study or grant end date, whichever is later.

13 ETHICAL CONSIDERATIONS

13.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with the principles set forth in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

13.2 INSTITUTIONAL REVIEW BOARD (IRB)

The Office of Human Research Ethics is responsible for ethical and regulatory oversight of research at UNC-Chapel Hill that involves human participants. The OHRE administers, supports, and guides the work of the Institutional Review Boards and all related activities. Any research involving human participants proposed by faculty, staff, or students must be reviewed and approved by an IRB before research may begin, and before related grants may be funded. OHRE and the IRBs are critical components of the coordinated Human Research Protection Program, which serves to protect the rights and welfare of human participants. All components of this program must work together to ensure institutional compliance with ethical principles and regulatory requirements. The following is a mission statement for the coordinated Human Research Protection Program:

The University of North Carolina at Chapel Hill is committed to expanding and disseminating knowledge for the benefit of the people of North Carolina and the world. An important part of that commitment to knowledge is research of the highest quality on all aspects of the health and behavior of people, and such research is only possible through the participation of humans as research participants. Human participants are partners in research and a precious resource to the university. At UNC-Chapel Hill, human participant research is a privilege, but not a right. Consistent with that philosophy, it is the mission of the UNC-Chapel Hill Human Research Protection Program to ensure that:

a. The rights and welfare of human participants are paramount in the research process;
b. The highest standards of ethical conduct are employed in all research involving human participants;
c. Research investigators are properly trained in the ethical and regulatory aspects of research with human participants;
d. Research investigators deal honestly and fairly with human participants, informing them fully of procedures to be followed, and the risks and benefits of participating in research; and
e. Research using human participants at UNC-CH conforms to applicable local, state, and federal laws and regulations and the policies of the university.

13.3 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks of TMS and tDCS will be provided to the participants. Consent forms describing, in detail, the study intervention, device, procedures, and risks are given to the participant and written documentation of informed consent is required prior to the administration of any assessments used in this study. All consent forms will be IRB-approved and updated with any new information as modifications are made throughout the study.

Together, the researcher and potential participants will review the study in its entirety by reviewing the consent form together in a private location. At several intervals during the consent review, the researcher will ask the

participant questions that will assess the comprehension of the information in the consent. If the participant is unsure or does not know, the researcher will return to that section and more carefully explain the information. Participants must sign the informed consent document prior to any procedures taking place. If needed, the participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records.

13.4 EXCLUSION OF WOMEN, MINORITIES, AND CHILDREN (SPECIAL POPULATIONS)

Non-English speaking individuals are excluded because the ability to accurately and complete communicate study information, answer questions about the study, and obtain consent is necessary. Pregnant participants will be excluded despite the fact that theoretical risk to mother or fetus is exceedingly small, since no safety data for pregnancy is known to exist for transcranial magnetic/electrical stimulation studies.

13.5 PARTICIPANT CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the research team. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants.

All data will only be referenced by dummy identifier code. Data will be stored on a password protected computer. A key connecting names and code numbers will be kept in a locked cabinet, accessible only by research personnel. All data will be stored and analyzed on password protected computers, also only accessible by research personnel. Participants will not be identified in any report or publication about this study. See *10 Data Handling and Record Keeping* for more information on source documentation storage and security.

13.6 STUDY DISCONTINUATION

In the event that the study is discontinued, participants who have completed or who are still enrolled in the study will be notified. Any new information gained during the course of the study that might affect participant's willingness to continue will be communicated within 2 days of the PI learning this information.

14 PUBLICATION POLICY

There are no restrictions on publications since this is an investigator-initiated study funded by a grant agency that has no influence on the publications resulting from this study.

15 LITERATURE REFERENCES

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APPENDIX A: SCHEDULE OF EVENTS

A detailed schematic describing phone screening and visit for stimulation.

Procedures	Phone Screening	Stimulation
Provide Verbal Consent	x	
Signed Consent Form		x
Assessment of Eligibility Criteria	x	x
Review of Medical History	x	x
Review of Concomitant Medications	x	x
Stimulation		x
Stimulation Questionnaire		x

APPENDIX B: IRB AMENDMENT TRACKING LOG

Change Initiated By:		Description of IRB: Type and Brief Summary	Date Submitted to IRB	Date of IRB Response	Requires Stipulations? (Y/N)	Requires Updated Consent Form? (Y/N)	Stipulation Submission Date	IRB Approval Date
Initials	Reference ID							

APPENDIX C: INFORMED CONSENT QUIZ

Name of Research Study:

You have been asked to be in a research study. This sheet will help you think of questions to ask but you may have other questions. This is not a test. We want to be sure you understand what it means to be in this research study. You should understand the research before you decide whether or not to participate.

1. What is the purpose of the research?

2. What are the possible risks of the research?

3. Does in the research cost me anything extra?

4. Can you stop being in the research once you've started?

5. Who will view your medical records?

6. Who do you call if I have questions about being a research subject?

7. Any questions?

APPENDIX D: NOTE TO FILE

IRB#: 17-0149 PI: Flavio Frohlich

Study Title: [Insert Short Name]

Researcher: _____ Date of Occurrence: _____

Participant ID: _____

Reason for Note:

_____
_____

Note:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Corrective action (if applicable):

_____
_____
_____

Signature: _____ Date: _____

APPENDIX E: TELEPHONE SCRIPT

Hello, my name is _____ and I am a _____ from the University of North Carolina at Chapel Hill conducting a research study about individuals with transcranial magnetic stimulation and transcranial direct current stimulation. Based on your history, you may be eligible to participate in our study.

Do you have time now to hear about the study, answer a few screening questions?

(If 'No', ask for a good time to call back)

(If 'Yes', proceed)

Great! This study is looking at motor activity in your hand caused by weak brain stimulation in healthy individuals. Findings from this study will help the development of new study using magnetic and electrical stimulations. In this study, a very weak electric current will be applied to your scalp. Some people report a mild tingling because of this stimulation, but no other side effects have been found. It is not a shock and should cause no pain.

Participation in this study includes only one session, which is stimulation session. You will be compensated for your time spent participating in the study. The maximum compensation for this study is XXXXXXX for completing one-day session. Are you still interested in participating?

(If 'No', thank them for their time; if 'Yes', proceed)

Great! In order to make sure you're eligible for the study, I need to ask you a few questions. Please answer yes or no. You do not need to provide any further details.

(If the answer given is not the same as the answer shown, thank the individual for his or her interest and say, unfortunately, they do not qualify for the current study)

- Are you between 18 to 50 years old? (Yes)
- Have you ever, or are you currently being treated for a neurological condition (e.g., epilepsy, migraines)? (No)
- Are you currently taking medication for the treatment of chronic pain or any other psychiatric illness? (No)
- Have you ever had brain surgery? (No)
- Do you have any brain devices or implants, including a cochlear implant or aneurysm clip? (No)
- Have you ever been diagnosed with a traumatic brain injury? (No)

Phone Screening:

☐ Pass
☐ Fail

Reason for failing: _____

_____

_____

Initials _____

You are eligible for participation in the stimulation session of the study.

Scheduled Stimulation Session

Date: _____

Time: _____

I will send you an email confirming this time, and providing directions on how to find the specific location of your session. We will also send you an email to confirm your appointment 24 hours beforehand. Please respond to this email so we know you are still coming. If you have any questions before then, please don't hesitate to contact us at this phone number or at sangtae_ahn@med.unc.edu. Thank you for your time.