# A PILOT STUDY INVESTIGATING THE EFFECTS OF CROSS FREQUENCY TRANSCRANIAL ALTERNATING CURRENT STIMULATION ON CORTICAL OSCILLATIONS UNDERLYING COGNITION

# STUDY CODE: "2PAC"

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|---|---|
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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event/Adverse Experience |
| ANOVA | Analysis of Variance |
| BAS | Behavioral Approach System |
| BIS | Behavioral Inhibition System |
| CFR | Code of Federal Regulations |
| CF-tACS | Cross frequency transcranial alternating current stimulation |
| CNS | Central Nervous System |
| Co-I | Co-Investigator |
| CRF | Case Report Form |
| CTRC | Clinical Trials Research Center |
| DMV | Department of Motor Vehicles |
| eCRF | Electronic Case Report Form |
| EEG | Electroencephalogram |
| ECG | Electrocardiogram |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| Hz | Hertz |
| ICF | Informed Consent Form |
| LAR | Legally Authorized Representative |
| NIBS | Noninvasive Brain Stimulation |
| NIH | National Institutes of Health |
| NRB | Neurosciences Research Building |
| OHRE | Office of Human Research Ethics |
| OHRP | Office for Human Research Protections |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| SAE | Serious Adverse Event/Serious Adverse Experience |
| tACS | Transcranial Alternating Current Stimulation |
| tDCS | Transcranial Direct Current Stimulation |
| 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** | *A pilot study investigation the effects of cross frequency transcranial alternating current stimulation on cortical oscillations underlying cognition* |
| **Short Title** | *2PAC* |
| **Protocol Number** | *Version 3.0* |
| **Phase** | *Pilot* |
| **Methodology** | *Double-blind, randomized, active sham controlled* |
| **Study Duration** | *This study will take two months to complete.* |
| **Study Center(s)** | *This is a single-site study performed at the University of North Carolina at Chapel Hill.* |
| **Objectives** (Purpose) | *The primary objective of this study is to explore the effect of transcranial random noise stimulation on oscillations underlying cognition* |
| **Number of Subjects** | *24* |
| **Diagnosis and Main Inclusion Criteria** | *Eligible participants will be healthy adults between the ages of 18-35 with no history of mental or psychiatric disorder.* |
| **Description of Intervention** (Procedures/methods) | *The participants will be randomized into one of three arms: either 40 minutes of sham tACS or 40 minutes of theta-gamma tACS or 40 minutes of delta-beta tACS while performing a cognitive control task.* |
| **Related IRB Applications** | *N/A* |

# 1 KEY ROLES

## 1.1 INDIVIDUALS

| | |
|---|---|
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## 1.2 INSTITUTIONS

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## 1.4 FUNDING SOURCES

Please list below the funding sources for this project:

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**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

Noninvasive brain stimulation (NIBS) methods have recently been gaining acceptance and attention as treatment strategies for many neurological and psychiatric disorders as well as improving cognition. The methods include well studied methods such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) as well as novel methods like transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS) and cross-frequency transcranial alternating current stimulation (CF-tACS). In particular, CF-tACS has been used to improve working memory capacity (Alekseichuk et al. 2017). CF-tACS was designed to target naturally occurring cross-frequency electrical coupling that is witnessed in a variety of cognitive tasks, such as episodic memory encoding (Poeppel et al. 2016), decision-making (Arnal et al. 2015), and attention (Quax et al. 2017). Recent evidence has even suggested that cross-frequency coupling underlies the relief from the symptoms of Parkinson's disease experience by patients with chronically implanted deep brain stimulators (deHemptinne et al. 2015). Cross-frequency coupling of neural oscillations is a relatively novel model of brain activity that has been gaining empirical traction over the past decade (see Canolty & Knight 2010 for review).

Oscillations are periodic electrical activity observed both intracranially and transcranially in humans using electrocorticograms (ECoG), electroencephalograms (EEG), magnetoencephalograms (MEG) (Buzsaki, Anastassiou, & Koch, 2012). Oscillations have been demonstrated to modulate neuronal firing, organize communication within and between brain regions and hence coordinate cognition (Fries, 2005; Frohlich & McCormick, 2010; Jensen & Mazaheri, 2010). Oscillations in the frequency bands 4 – 8 Hz and 8 – 12 Hz (often referred to as theta and alpha band) have been shown to be correlated with working memory performance (Jensen, Gelfand, Kounios, & Lisman, 2002; Jensen & Tesche, 2002; Raghavachari et al., 2001) and cognitive control (Cavanagh & Frank, 2014). Thus, changes in cognitive performance could be reflected in changes in oscillations. The current study aims to test for the role of cross-frequency coupling in cognitive processes.

We will be collecting a saliva sample at the first session. This sample will be used to test for a single nucleotide polymorphism in the BDNF gene whose presence may have an influence on effectiveness of brain stimulation. Within the central nervous system, BDNF regulates survival, proliferation, and synaptic growth as well as directly influences synaptic plasticity in the adult human brain (Antal et al., 2010). Egan et al. (2003) demonstrated that Val66Met, a single nucleotide in the BDNF gene, has function consequences in healthy humans, including decreased episodic memory and hippocampal inducing a reduction in recall capacity. This polymorphism is common in over one third of the Caucasian population (65% Val66Val to 35% Val66MET) (Pezawas et al, 2004; Hariri and Weinberger, 2003). Kleim et al. (2006) found that individuals with the Val/Val polymorphism respond to tDCS and transcranial magnetic stimulation (TMS) treatments with expected change, whereas, individuals expressing Val/MET allele do not. These authors indicate the difference to be caused by the impairment in synaptic plasticity caused by the Val/MET allele. These findings suggest that individual efficacy of treatments using brain stimulation may be partially genetically predetermined and should be taken into account when preforming such procedures. Accordingly, we will conduct genotyping of all participants in this study in order to assess BDNF status.

In addition to BDNF, we will be assessing sex hormone levels in our participants before stimulation. Cortical excitability has been shown to depend on the phase of the menstrual cycle in women (Smith et al. 1999, Badawy et

al. 2013, Walpurger et al. 2004). This effect may be mediated by sex hormones (e.g., estradiol, progesterone, testosterone, androstenedione). To account for the different levels of sex hormones in participants when they arrive for the experimental sessions, we will collect saliva for assessing levels of estradiol, progesterone and testosterone. In addition, we will ask women information on birth control use and the best guess-estimate of first day of last menstrual cycle.

## 2.2 INVESTIGATIONAL AGENT

CF-tACS involves the application of electric current on the scalp in a waveform that emulates the coupling between two frequencies: a higher frequency waveform is nested in the peak of lower frequency waveform (Alekseichuk et al., 2016) and has previously been demonstrated to increase performance during a working memory task.

## 2.3 DOSE RATIONALE

The primary rationale for the dose is the duration of the cognitive tasks that we require the participants to perform during stimulation. The task takes about 40 minutes total and is broken up into 8 blocks. The activity from the brain is unable to be accurately recorded during the stimulation itself, so we have included resting-state periods after each block of the task with stimulation to allow for analysis of brain activity (see Alekseichuk et al., 2016 for similar methods). Moreover, our lab has successfully performed many transcranial electrical stimulation experiments where stimulation duration has been 40 minutes (IRB # 14-1622, 16-1911) and no significant side effects have been observed.

## 2.4 STUDY AIMS/HYPOTHESES

The purpose of this pilot study is to evaluate the potential efficacy of using CF-tACS to modulate cortical oscillations observed during cognitive tasks, to generate hypotheses, and to obtain statistical estimates and other information needed for planning a subsequent larger-scale study.

Aim 1. Characterize CF-tACS effects in terms of the outcome measures of interest.

Aim 2. Perform exploratory analyses to generate new hypotheses.

Aim 3. Obtain preliminary data and population parameter estimates needed to plan a future study.

# 3 SUBJECT SELECTION AND WITHDRAWAL

A total of 24 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:

- Between the ages of 18 and 35 years
- Able to provide 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 through self-report will be excluded from participation in the study:

- 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, malignancy)
- Prior brain surgery
- Any brain devices/implants, including cochlear implants and aneurysm clips
- History or current traumatic brain injury
- (For females) Pregnancy or breast feeding
- Personal or family history of mental/psychiatric disorder (e.g., anxiety, major depressive disorder, schizophrenia, etc.)
- Positive urine test for the following: Marijuana (THC), Cocaine (COC), Phencyclidine (PCP), Amphetamine (AMP), Ecstasy (MDMA), Methamphetamine (Mamp), Opiates (OPI), Oxycodone (OXY), Methadone (MTD), Barbiturates (BAR), Benzodiazepines (BZO), Buprenorphine (BUP), Tricyclic Antidepressants (TCA), Propoxyphene (PPX)
- 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:** There are no exclusion criteria based on race, gender, or ethnicity. However, 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. This may skew enrollment away from Hispanic/Latino population.

**Justification for excluding women or women who become pregnant:** Pregnant participants will be excluded out of an abundance of caution despite the fact that theoretical risk to mother or fetus is exceedingly small, since no safety data for pregnancy are known to exist for CF-tACS studies and only limited safety data for other noninvasive brain stimulation methods like TMS (Sayar et al. 2014) . We will verify pregnancy status via a urine pregnancy test for all female participants prior to receiving treatment on Day 1 of Stimulation.

At the beginning of Sessions 2, 3 and 4, female participants will be asked if there is a possibility that they might be pregnant since Session 1. If the participants answer 'Yes' or 'Maybe', pregnancy test will be conducted. A pregnancy questionnaire will be used to document the answers.

Sayar, G. H., Ozten, E., Tufan, E., Cerit, C., Kaan, G., Dilbaz, N., & Tarhan, N. (2014). Transcranial magnetic stimulation during pregnancy. Archives of women's mental health, 17(4), 311-315.

## 3.3 STRATEGIES FOR RECRUITMENT AND RETENTION

### 3.3.1 RECRUITMENT

The target population of this study includes healthy individuals between the ages of 18 to 35 recruited from UNC Chapel Hill and the surrounding area, including approximately 30,000 candidates for participation. Recruitment will occur via two methods: flyers to be distributed at major locations on the campus (libraries, gyms, classroom buildings, etc.) and a mass email to all individuals with a UNC-affiliated email address.

### 3.3.2 RETENTION

The retention strategy includes a payment schedule of four times per participant, corresponding with the four sessions. Payment is increased for each session to incentivize completion of the study. Individuals who complete both sessions will receive a non-coercive bonus payment, as well. Research staff will send participants a reminder text the day before each session, and will be available by email and phone at all times.

# 4 BASIC STUDY DESIGN

The design for this study is a pilot, randomized, double-blind, sham-controlled, crossover clinical trial which will be used to demonstrate feasibility and collect effectiveness data for further refinement of CF-tACS approach and for the subsequent design of a follow-up, multi-site, large scale study. We are seeking 24 healthy participants, both male and female, between the ages of 18-35. All women of child-bearing potential (defined as menstruating women of all ages) will be asked to take a pregnancy test during the initial session in order to determine eligibility for the study. We estimate 2 months to complete study enrollment.

The experimental design is a 3-treatment, 3-period, 3-sequence crossover with a 1 week washout interval between periods. N=24 participants will be enrolled and allocated by stratified randomization to six treatment sequences, S-At-Ad, S-Ad-At, At-S-Ad, At-Ad-S, Ad-S-At, Ad-At-S. S refers to Sham Regimen which is 40 minutes of sham CF-tACS, At refers to Active Theta-Gamma Frequency Regimen which is 40 minutes of verum CF-tACS, and Ad refers to Active Delta-Beta Frequency Regimen which is 40 minutes of verum CF-tACS.

Participants will be randomly assigned to one of 6 sequences on the first visit.

Sham treatment will include 10 seconds of ramp-in to 1 minute of CF-tACS with a ramp-out of 10 seconds for a total of 80 seconds of stimulation. The 80 seconds of stimulation serves to desensitize the scalp beyond which participants are generally not able to tell apart the presence or absence of stimulation. This strategy has been described is previous studies using tACS (Alekseichuk et al. 2017; Mellin et al. 2018). Verum CF-tACS will have a 10 second ramp-in and ramp-out with 5 minutes of stimulation, for 8 separate blocks with a minimum 3 minute break between each block, for a total of 2560 seconds of stimulation. Stimulation waveform is coupled frequency with a low frequency component and brief high frequency component on each cycle with maximum amplitude of 2 mA.

Eligible participants will have a total of 4 visits, each lasting approximately 3 hours and separated by at least 1 week. Total participation will include about 12 hours over the course of four weeks. All time estimates take into consideration breaks and time variance in administration.

## 4.1 TREATMENT ASSIGNMENT PROCEDURES

Participants will be randomized into one of 6 sequences. This is a double-blind study, so neither the participant nor the researcher will know which treatment the participant is receiving, if any.

### 4.1.1 RANDOMIZATION PROCEDURES

Sangtae Ahn will randomize 24 6-digit stimulation codes which will be used by the study coordinator and research assistants and will be linked to the participant numbers of enrolled participants. These stimulation codes are directly linked to which treatment participants receive (sham CF-tACS, theta-gamma verum CF-tACS, or delta-beta CF-tACS) at each session, and will be used with the NeuroConn stimulator. An unblinded code sheet that matches these stimulation codes to treatment arm will be kept by Sangtae Ahn and will not be available to the study coordinator or research assistants. Sangtae Ahn will not be involved in data collection, interaction with participants or data analysis ensuring double-blind.

The unblinded code sheet will have the following information:

· The initial identifier codes for all potential participants

· Stimulation code: 6-digit numerical code for the stimulation session

· Condition number: Numerical code for the condition

· Condition name: Name of the condition

A copy of this code sheet with condition number and condition name REMOVED is provided to the study coordinator and research assistants. This blinded code sheet will be used to ensure the correct stimulation code is provided for each session.

These linked codes ensure that the study coordinator and research assistants are kept blinded to which treatment each participant receives. Please see Data and Safety Monitoring for more information on unblinding this information.

### 4.1.2 DROPOUTS

In case of dropouts, defined as not completing the stimulation part of either visits, data will not be included in the final analysis and the stimulation codes will be reused for the next participants.

# 5 STUDY SCHEDULE

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

The screening process will involve a telephone call with the potential participant to inform of expectations and determine eligibility. A researcher will conduct a screening with each participant prior to scheduling the first session. If a participant is determined to be ineligible, contact information and screening question answers will be retained to avoid rescreening the participant. All data retained will be deidentified.

## 5.2 STIMULATION SESSIONS

Participants will undergo four sessions with the same procedure; the only change will be the stimulation condition. In the initial session, participants will have the procedure explained and reminded of their expectations and rights (informed consent). After obtaining consent, a urine drug test and pregnancy screening will be administered. Sessions 2, 3, and 4 will be the same as session 1, except there will be no CF-tACS stimulation during session 1.

### 5.4.1 SESSION 1

In the initial session, participants will be explained the procedure and reminded of their expectations and rights (informed consent). After obtaining consent, a urine drug test and pregnancy screening will be administered.

- Preparation - Once a negative pregnancy test and negative drug test are confirmed, , the stimulation electrodes, EEG net, ECG electrodes and respiration belt will be applied.
- Questionnaires - The participant will fill out a series of questionnaires pertaining to self-reported handedness, affect, behavioral traits and sleep quality.
- Saliva collection - Saliva will be collected for BDNF genotyping and sex hormone level measurement.
- Resting state EEG – Participant will be asked to relax with eyes open and EEG will be collected simultaneously
- Practice cognitive tasks - The participant will perform a shortened version of the cognitive tasks as practice from which baseline performance will be assessed.

· Following the practice, the participant will receive 40 minutes of either verum CF-tACS or sham CF-tACS stimulation, depending on the randomized condition. During the stimulation, the following procedures will be followed

A. Cognitive Control Task – Participant will perform a cognitive control task for 5 minutes. CF-tACS will be delivered during these 5 minutes. There will be no CF-tCS during session 1.

B. Resting state EEG - Participant will be asked to relax with eyes open and EEG will be collected simultaneously for 3 minutes. There will be no CF-tACS during this time. Subject are allowed to take more (but not less) than 3 minutes of rest if desired.

• Repeat steps A and B 8 times until all conditions of the Cognitive Control Task are finished

Following the end of stimulation,

• Electrodes and net will be removed and participant can wash their hair and face

• Participant will receive compensation that scales with the session number to incentivize study completion. Session 1 will be paid $20, session 2: $30, session 3: $40, and session 4: $50.

### 5.4.2 UNBLINDING PROCEDURES

There are no current plans to systematically unblind participants to the treatment they may or may not have received during the clinical trial. However, following the completion of data collection, participants may contact the Frohlich Lab for unblinding information.

# 6 STUDY PROCEDURES/EVALUATIONS

## 6.1 SELF-REPORT MEASURES

During the telephone screening, researchers will collect demographics, which include medical history and medication history. In addition, several other self-report measures will be used throughout this study. These measures are listed below and can be found in the attached documents.

A. The State-Trait Anxiety Inventory (STAI) is a 20-item self-report assessment that assesses either temporary or chronic anxiety. For the purposes of this study, the state version will be used to measure anxiety as a result of the stress condition. The STAI is commonly used to assess both types of anxiety, and has applications in both clinical and research settings (Spielberger et al, 1983).
B. The Pittsburgh Sleep Quality Index (PSQI) is a 14-item self-report assessment used to assess an individual's sleep quality from poor to good. This scale is widely used and has been demonstrated to produce reliable data (Buysse et al, 1989).
C. The Behavioral Inhibition and Behavioral Approach System Scales (BIS/BAS) are a set of 24 questions used to assess an individual's sensitivity to approach vs. inhibition in motivating behavior. This scale is commonly used to measure behavior and has been demonstrated to be reliable (Carver & White, 1994).
D. The Positive and Negative Affect Schedule (PANAS) is a 20-item self-report assessment using a 5-level Likert scale to assess the positive and negative affect of an individual over the past week. This scale has been shown to be a reliable measure of both positive and negative affect with little subjectivity to demographic variables (Watson et al, 1988).
E. The Edinburgh Handedness Inventory is a 20-item scale to assess the hand dominance of a person in everyday activities (Oldfield, 1971)
F. Beck's Depression Inventory is a 21-item scale to assess the relative presence of depressive symptoms

## 6.2 SPECIAL ASSAYS OR PROCEDURES

Each participant will receive stimulation on three days, separated by a week. Two session will involve verum CF-tACS, and the other will involve sham tACS; the order of stimulation condition will be randomized for each participant. For more information on the stimulation procedures, see section *8.2 Preparation and Administration of Study Investigational Product*.

## 6.3 SAFETY MEASURES

We will be monitoring the safety of our participants throughout the study with the following measures. These measures are listed below and can be found in the attached documents.

A. A stimulation adverse effects questionnaire used in previous studies (IRB #14-1622, #14-3285, and #14-0600) will be administered at the end of each stimulation session. This questionnaire will be used as a safety measure and to collect data on participant experience. Please see *10.1 Safety Parameters* for more information.

## 6.4 LABORATORY EVALUATIONS

### 6.4.1 SCREENING LABORATORY EVALUATIONS

A urine pregnancy test will be performed for all female participants. All participants will also undergo a urine drug test.

INSTRUCTIONS FOR SPECIMEN PREPARATION, HANDLING, AND STORAGE. For this evaluation, an FDA approved commercial home-based kit will be used (HCG Urine Pregnancy Test Strip). Results are available after only a few minutes. Once the results are clear, the researcher will make a note and the sample will be disposed. All samples will be handled using single-use disposable medical gloves.

### 6.4.2 SALIVA SAMPLES

INSTRUCTIONS FOR SPECIMEN PREPARATION, HANDLING, AND STORAGE. The saliva sample will be collected using 2mL DNA collection kit from DNA Genotek. Before sample collection, it is imperative that the participant does not eat, drink, smoke or chew gum for at least 30 minutes before providing a sample. Once the participant provides the 2ml sample, the collection tube is closed and a liquid from the lid will be released into the tube. The original lid will be removed and replaced with a small cap and the tube will be agitated for 5 seconds. The sample is then returned to the plastic packaging and labeled with the date of collection, the study name, and the participant ID. These samples are kept in a secure location at room temperature until the completion of data collection. Once data collection is complete, the PCR will be performed at the UNC Biospecimen Processing Facility and Sangar sequencing will be done by GENEWIZ.

INSTRUCTIONS FOR SPECIMEN PREPARATION, HANDLING AND STORAGE FOR SEX HORMONE TESTING. Saliva will be collected using SalivaBio Passive Drool Method. The same restrictions that apply for saliva samples for DNA testing apply here as well. 2ml sample will be collected in a cryovial and froze at -20° C at a secure location. In contrast to saliva for genotype testing, no preservatives are used. Once data collection is done, the samples will be analyzed for levels of estradiol, progesterone and testosterone by Salimetrics. The samples being sent will be deidentified.

## 6.5 COGNITIVE TASKS

### 6.5.1 COGNITIVE CONTROL TASK

The cognitive control task is a well-established task in functional magnetic resonance imaging (Koechlin et al. 2003; Badre & D'Esposito 2007), electrocorticography in epileptic patients undergoing surgery (Voytek et al. 2015), and causal testing in stroke patient populations (Badre et al. 2009). The task involves a series of rules that are required to select an appropriate action. In the simple cognitive control conditions, there is a clear mapping of stimulus to response. In the complex cognitive control conditions, there are context rules that change the lower level rules that must be followed. Previous research using this task shows cross-frequency coupling as measured by electroencephalography (EEG) that will be targeted by the CF-tACS proposed here (Riddle et al. in preparation).

# 7 STUDY OUTCOMES

## 7.1 PRIMARY OUTCOMES

The cognitive task will consist of 400 trials. The EEG recorded simultaneously with the task will be analyzed following an established preprocessing pipeline to remove artifacts related to eye movements, eye blinks, heart beats and muscle activity. The oscillation power and phase will be estimated using Morlet wavelet convolution. The primary outcome is phase-amplitude coupling between the stimulated frequencies (measured from EEG), reaction time, and accuracy. Phase amplitude coupling will be calculated using the phase locking value z-corrected based on a boot-strapped null distribution from randomly shifting the amplitude values 1000 times (see Cohen *Analyzing Neural Time Series Data* 2014 for method).

Our primary outcomes:

- Theta-gamma tACS will increase theta-gamma phase amplitude coupling (one-tailed, Student's t-test)
- Delta-beta tACS will increase delta-beta phase amplitude coupling (one-tailed, Student's t-test).
- Theta-gamma tACS will alter behavior (reaction time or accuracy) as a function of set-size (Student's t-test).
- Delta-beta tACS will alter behavior (reaction time or accuracy) as a function of abstraction (Student's t-test).

## 7.2 SECONDARY OUTCOMES

The following will be assessed as secondary outcomes

- Brain behavior correlation to account for inter-participant variance. For the significant behavioral findings, we will correlate the strength of phase amplitude coupling during the post-stimulation rest period with the impact on behavior.
- For the significant behavioral findings, brain behavior correlation between the strength of phase amplitude coupling in the baseline session to the behavioral effect of CF-tACS on task performance.

## 7.3 EXPLORATORY OUTCOMES

Additionally, the following exploratory measures will be assessed

- Modulation in spectral power in other frequency bands (1 – 4 Hz; 8 – 12 Hz; 12 – 30 Hz; 30 – 50 Hz) of CF-tACS
- Coherence between distant regions of the brain in the slower frequency of the CF-tACS coupled pair (delta and theta)
- Hormone level and BDNF as covariates in analysis of differences in spectral power
- Self-reported anxiety, affect and sleep quality as covariates in the analysis of differences in spectral power

# 8 STUDY INVESTIGATIONAL PRODUCT

## 8.1 DEVICE DESCRIPTION

Participants will be stimulated with the commercial, CE-certified Neuroconn Plus stimulator. The use of this device in this study has previously received a NSR designation on initial review by the full UNC IRB. The NeuroConn device description is as follows:

The DC-STIMULATOR is a CE-certified medical device for conducting non-invasive transcranial direct-current stimulation (tDCS) in humans. DC stimulation is used in clinical practice and in the research of stroke, epilepsy, migraine, tinnitus, depression, multiple sclerosis, dementia and chronic headache. The DC-STIMULATOR is a micro-processor-controlled constant current source. It meets the highest safety standards thanks to (hardware- and software-based) multistage monitoring of the current path. By continuously monitoring electrode impedance it can detect insufficient contact with the skin and automatically terminate stimulation, maximizing patient safety.

The device's alphanumeric display and the 4 touch keys allow various stimulation modes to be selected and stimulation parameters such as current strength, duration, fade-in and fade-out to be set.

DC-STIMULATOR features:

- 1 channel (anodal and cathodal stimulation possible)
- Adjustable current up to 5,000 µA *
- Adjustable application time up to 30 minutes *
- 2 standard modes - single (continuous stimulation) and - pulse (cyclical stimulation activation/deactivation) with fade in and fade out
- Customer-specific programs possible (optional)
- "Study mode" for blind processing of genuine and 'pseudo' stimulation (optional)
- External trigger input (optional)

## 8.2 SAFETY FEATURES

The Neuroconn DC Plus stimulator has been cleared for investigational use by the FDA and is CE-Certified. More information can be found in the manual for the stimulator.

## 8.3 PREPARATION AND ADMINISTRATION OF STUDY INVESTIGATIONAL PRODUCT

After participants have completed the questionnaires, they will be comfortably seated. The research team will first measure their heads electrode placement using the 10-20 system. Participants will then be fitted with the 3 electrodes for stimulation. The participant will be in the relaxed yet, experimentally controlled state with their chin on a chin rest in front of a monitor. Participants will wear earplugs throughout the session to reduce distraction. One session of stimulation will be performed per visit for 40 minutes, in 8 blocks of 5 minutes each. During the verum CF-tACS conditions, participants will have a 10 second ramp in and ramp out with 5 minutes of stimulation for 8 blocks for a total of 2560 seconds. Stimulation waveforms are cross frequency waveforms with a burst of either beta (18-35 Hz) or gamma (30-60Hz) frequency at the peak of a slower oscillations in delta (2-5 Hz) or theta (4-8Hz). The maximum amplitude of stimulation is 2 mA. The sham CF-tACS stimulation will include 10 seconds of ramp in to 20 seconds of CF-tACS with a ramp out of 10 seconds for a total of 40 seconds of stimulation. Electrodes

(3.0 cm x 3.0 cm) will be affixed using electrically conductive ten20 paste and placed over F4 and C4. A single return electrode (5.0 cm x 7.0 cm) will be affixed in the same manner between Cz and Fz.

Our stimulation setup consists of the stimulator controlled by a desktop through a USB DAQ (National Instruments). Stimulation parameters (waveform, duration, amplitude) is set by custom written software application that is preprogrammed for each study. The software receives stimulation codes and generates the stimulation waveform and sends it to the stimulator where the waveform is converted to stimulation current. The mapping between stimulation code and stimulation waveform is hidden from the experimenter and only the study member (Sangtae Ahn) will be able to access this.

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. *Please see Appendix F for an example of the training documentation log.* To monitor side effects of stimulation a questionnaire will be administered after each stimulation session. *Please see Attachment 1 for an example of the stimulation questionnaire.*

## 8.4 ASSESSMENT OF PARTICIPANT COMPLIANCE WITH STUDY INVESTIGATIONAL PRODUCT

Compliance for this study includes attending all four sessions. Individuals who miss the first session (and are unable to reschedule) and/or individuals who miss the second, third or fourth session (and are unable to complete the remaining sessions) will be dropped from the study.

# 9 POTENTIAL RISKS AND BENEFITS

## 9.1 BENEFITS TO SUBJECTS AND SOCIETY

The results of this study have implications for the use of CF-tACS as a treatment method for cognitive deficits and other neurological and psychiatric disorders. The results of this study may also prompt further investigation into the relationship between cortical oscillations and brain stimulation waveforms.

This study is not designed to benefit the individual participants.

## 9.2 POTENTIAL RISKS

### 8.2.1 PHYSICAL

**Risk of Injury and Discomfort**: Transcranial current stimulation has been used without any reports of serious side-effects for more than a decade. This stimulation made has NOTHING to do with electroconvulsive therapy that applies many orders of magnitude higher stimulation current. Rather, transcranial current stimulation is so weak that it does not cause super-threshold activation of neurons (Frohlich and McCormick, 2010). In particular, tACS has been used without reports of any serious side-effects. 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 an adverse 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 the participant experiences severe discomfort, the stimulation will be immediately stopped and the participant will withdraw from the study.

## 9.3 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 patients with personal and family 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 patient 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 session. Following the conclusion of the stimulation session, the participant will receive an Adverse Effects Questionnaire to report on any of the side-effects he/she may have experienced. This questionnaire reports side-effects on a likert scale (1=Absent, 2=Mild, 3=Moderate, 4=Severe). If the participant reports side-effects of Moderate to Severe intensity, a study coordinator or research assistant will discuss the side-effects experienced and note this response. If the participant has rated Severe discomfort, the participant will be withdrawn. The PI will be contacted based on the reported intensity on the Adverse Events Questionnaire and the participant's verbal confirmation of intensity.

### 9.3.1 PREGNANCY FOLLOW-UP

Every female participant will take a pregnancy test on Day 1 of Stimulation. If, after testing negative at Day 1 of Stimulation (meeting inclusion criteria), a participant reports becoming pregnant during the course of the study, she will be withdrawn from further participation. There are no plans to follow participants who become pregnant while enrolled in the study.

# 10 DATA AND SAFETY MONITORING

## 10.1 FROHLICH LAB MONITORING PLAN

The purpose of this monitoring plan is to present the Frohlich Lab's approach to monitoring clinical trials. The plan facilitates compliance with good clinical practice (GCP):

a. The rights and well-being of human subjects are protected.
b. The reported trial data are accurate, complete, and verifiable from source documents
c. The conduct of the trial is in compliance with the currently approved protocol/amendment(s) with GCP, and with applicable regulatory requirement(s)

This section identifies key monitoring activities and specifies the data to be reviewed over the course of a clinical trial. This is a single site, investigator-initiated, clinical trial, so there will be no site monitoring plan in place.

The latest version of the approved IRB application for this clinical trial will be followed at all times. This responsibility falls into the hands of the study coordinator and research assistants. If at any time there is a deviation from protocol, the deviation from protocol log will be filled out. All team members will be trained on how and when to use this log. The most up-to-date IRB application will be on file in the Clinical Trials office in Room 233 of the Medical School Wing C. Deviations will be sent to the IRB every 4-6 weeks (if necessary).

Periodically, study staff should review 3 randomly selected informed consent forms to ensure that (1) these forms have been filled out appropriately, and (2) the consent form process was followed and properly documented. Should any consent form be in violation, the research team will perform and document a complete review of all consent forms.

Given that we are not sampling within a clinical population we do not expect suicidal ideation to be a concern. However, we will review the Beck's inventory within 24 hours and if there is any indication that a person is a danger to themselves we will notify the medical director of the Carolina Center for Neurostimulation, Dr. Fryml, who will respond appropriately.

AE and SAE are clearly defined in this document. Documents of AE and SAE can be found in the study binder on file in the Clinical Trials office in Room 233 of the Medical School Wing C. It is the responsibility of the study coordinator to report all events to the PI in a timely manner (see *9.3 Reporting Procedures*). All AEs and SAEs will be discussed with the PI. For our practices, we have adapted the decision tree provided by the UNC-CH IRB to assist with reporting of such events.

## 10.2 SAFETY OVERSIGHT

Safety oversight will be under the direction of the PI, who will review AEs in real time and make decisions regarding a participant's continuation of the clinical trial.

## 10.3 EARLY WITHDRAWAL OF PARTICIPANTS

### 10.3.1 REASONS FOR WITHDRAWAL

A study participant will be discontinued from further participation if:

- The participant fails to adhere to rules, including stress, exercise, and sleep restrictions

- 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 experience severe discomfort during stimulation

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

### 10.3.2 DATA COLLECTION AND FOLLOW-UP FOR WITHDRAWN PARTICIPANTS

We will collect safety data on any participant discontinued because of an AE or SAE. In any case, every effort will be made to undertake protocol-specific follow-up procedures. If an AE has been reported, researchers will help the participant seek the medical care they need and a follow-up will be performed by the PI. In the case of an early withdrawal, the researcher will make a note to file indicating this.

## 10.4 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 visits, 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, given that previous studies using tDCS in patients with depression and schizophrenia have had no seizures occur (Berlim et al., 2013, Brunelin et al., 2012).

The study will also be stopped (at least temporarily) if studies provide evidence that transcranial current stimulation caused brain damage or other harmful effects on subjects, either short-term or long-term. Examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events.

The reasons for stopping the study and asking for further investigation include:

- If a seizure occurs during a study visit, a temporary hold will be placed on the clinical trial

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).

Berlim, M. T., Van den Eynde, F., & Daskalakis, Z. J. (2013). Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Journal of psychiatric research, 47(1), 1-7.

Brunelin, J., Mondino, M., Gassab, L., Haesebaert, F., Gaha, L., Suaud-Chagny, M. F., ... & Poulet, E. (2012). Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. American Journal of Psychiatry, 169(7), 719-724.

# 11 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 Adverse Events, Serious Adverse Events, and Unanticipated Problems. This section is a reference for internal use.

## 11.1 SAFETY PARAMETERS

**STIMULATION SIDE EFFECTS.** A stimulation adverse effects questionnaire used in previous studies will be administered at the end of each stimulation session. This questionnaire will be used as a safety measure and to collect data on participant experience. The adverse effects questionnaire asks participants to respond on a 4-point Likert scale on the severity of symptoms experienced during the stimulation session (1 = absent, 2 = mild, 3 = moderate, 4 = severe). 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).

In addition to this survey, the study coordinator or research assistant will periodically check in with the participant during the stimulation session to assess side effects.

## 11.2 METHODS AND TIMING FOR ASSESSING, RECORDING, AND ANALYZING SAFETY PARAMETERS

### 11.2.1 ADVERSE EVENTS

All AEs, including local and systemic reactions not meeting the criteria for “serious adverse events”, will be captured on the appropriate CRF. In addition, the AE Report Form will be completed by the study coordinator (Appendix B). The AE Report Form includes the following:

- What is known about the therapy
- What is known about previous reported side effects
- If the AE occurred in temporal relation to the therapy
- Whether or not the AE improves or disappears when treatment is stopped
- Whether the AE is worsening of baseline symptoms
- Whether the AE is related to concurrent medical condition or medication use

Once complete, this form will be given to the PI and Co-I, who will review, comment, and sign this form. Completed forms will be placed in the participant’s folder.

In addition, the study coordinator will document any AE occurrence on the AE log (*Appendix D*), which includes information such as the date of the AE, severity, relationship to the treatment (assessed by the PI and Co-I*), actions taken, and outcome(s). The log will be reviewed and initialed by the PI 72 hours after being completed. All AEs occurring during the clinical trial will be documented appropriately regardless of relationship to CF-tACS. All AEs will be followed to adequate resolution and will be graded for severity and relationship to study treatment. Any medical condition noted at the initial session will be considered at baseline and not reported as an AE.

All AEs will be graded for severity using the following guidelines:

- **ASYMPTOMATIC**. The participant is exhibiting no symptoms due to this event; no treatment needed.
- **MILD**. Event results in mild or transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily activities (e.g., insomnia, mild headache)
- **MODERATE**. Event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (e.g., fever requiring antipyretic medication). In the case of a moderate AE, the medical advisor may recommend an over the counter medication.
- **SEVERE AND UNDESIRABLE**. Event results in significant symptoms that prevent normal daily activities; may require hospitalization or invasive intervention (e.g., anemia resulting in blood transfusion).

Changes in the severity of an AE will be documented with the Note to File document (Appendix E) and will be filed in the participant's folder.

***Relationship to Study Products**: The PI will determine whether an AE is associated with the study treatment. The event will be labeled associated if the event is temporally related to the administration of a therapy and no other factors can explain the event. The event will be labeled as not associated if the event is temporally independent of the study treatment and can be explained by external factors, such as major life events.

### 11.2.2 SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE): An SAE, as defined by the NIH, consists of adverse events that result in death, require either inpatient hospitalization or the prolongation of hospitalization, are life-threatening, result in a persistent or significant disability/incapacity or result in congenital anomaly/birth defect. Other important medical events, based upon appropriate medical judgment, may also be considered Serious Adverse Events if a trial participant's health is at risk and intervention is required to prevent an outcome mentioned.

All SAEs will be recorded on the Serious Adverse Events Form (Appendix B), documented in the UE/SAE log and reported to the IRB. The SAE Form will be completed by the study coordinator, and includes information relating to the onset and nature of the SAE, relationship to the study treatment, seriousness of the SAE, treatment required as a response to the SAE, and outcome. This form will be filed in the participant's folder at the resolution of the event. The study coordinator will complete the UE/SAE log (Appendix D) which includes information such as the date of the event, time at which the study team was informed of the event, details, when the IRB was notified, and the date that the SAE form was completed.

### 11.2.3 UNANTICIPATED PROBLEMS

Unexpected Events (UE) will be recorded on the UE/SAE log (Appendix D) 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, and whether the SAE form was completed. 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.

## 11.3 REPORTING PROCEDURES

We will be adopting the OHRE's "Reporting New Safety Information" SOP (SOP #1401):

| What Event is Reported | When is Event Reported | By Whom the Event is Reported | To Whom the Event is Reported |
|---|---|---|---|
| Fatal or life-threatening unexpected, suspected serious adverse reactions | Within **7 calendar days** of initial receipt of information | Investigator | UNC IRB |
| Non-fatal, non-life threatening unexpected, suspected serious adverse reactions | Within **7 calendar days** of initial receipt of information | Investigator | UNC IRB/Institutional Officials, DSMB |
| Unanticipated adverse device effects | Within **7 calendar days** of investigator first learning of effect | Investigator | UNC IRB |
| Unanticipated problem that is not an SAE | Continuing Review | Investigator | UNC IRB/Institutional officials |
| All protocol deviations that did not harm subject(s) or others or place subject(s) or others at increased risk of harm | Continuing Review | Investigator | UNC IRB |

### 11.3.1 REPORTING OF PREGNANCY

Pregnancy tests will be administered on Visit 1 of Stimulation to all women of child-bearing potential (CBP). Within the study target population (ages 18-35), menstruating females, regardless of age are considered "CBP". Women who have had a hysterectomy or a bilateral oophorectomy are not considered of "CBP". There are no studies that suggest CF-tACS would interfere with pregnancy. However, should a participant become pregnant during the study, her participation will be immediately terminated.

## 11.4 TYPES AND DURATION OF FOLLOW-UP OF PARTICIPANTS AFTER ADVERSE EVENTS

The study coordinator will follow up within one week of an adverse event by a phone call.

# 12 STATISTICAL PLAN

The statistician for this study is Dr. Justin Riddle.

## 12.1 STUDY HYPOTHESIS

*NULL HYPOTHESIS*. The change in task-performance for the cognitive control task is not significantly modulated by CF-tACS relative to sham tACS.

*ALTERNATIVE HYPOTHESIS*. CF-tACS induces an enhancement in task-performance during the cognitive control task by increase phase-amplitude coupling. This enhancement in performance is frequency specific. Theta-gamma CF-tACS modulates performance as a function set-size. Delta-beta CF-tACS modulates performance as a function of abstraction.

## 12.2 STATISTICAL ANALYSIS PLANS

Statistical analyses will be performed to test the null hypothesis indicated in section *2.4 Study Aims/Hypothesis*.

The cognitive task will consist of 400 trials. The EEG recorded simultaneously with the task will be analyzed following an established preprocessing pipeline to remove artifacts related to eye movements, eye blinks, heart beats and muscle activity. The oscillation power and phase will be estimated using Morlet wavelet convolution. The primary outcome is phase-amplitude coupling between the stimulated frequencies (measured from EEG), reaction time, and accuracy. Phase amplitude coupling will be calculated as the phase locking value corrected for spurious noise using a boot-strapped null distribution (see Cohen Analyzing Neural Time Series Data 2014 for method).

Our primary outcomes and their test are described below:

- Theta-gamma tACS will increase theta-gamma phase amplitude coupling (one-tailed, Student's t-test)
- Delta-beta tACS will increase delta-beta phase amplitude coupling (one-tailed, Student's t-test).
- Theta-gamma tACS will alter behavior (reaction time or accuracy) as a function of set-size relative to sham-tACS (Student's t-test).
- Delta-beta tACS will alter behavior (reaction time or accuracy) as a function of abstraction relative to sham-tACS (Student's t-test).

As exploratory analysis, linear mixed-effects models with BDNF genotype, sex hormone levels, as factors in addition to the variables condition and period will be fit with the rest of the analysis following what is described for primary analysis.

## 12.3 SAMPLE SIZE DETERMINATION

Based on the study by Alekseichuk et al 2017 which investigated the effect of CF-tACS on task accuracy and resting state EEG connectivity in 20 healthy participants per crossover arm, we conjecture that our effect size is at least 0.48. With this effect size, our sample size of 24 has power greater than 60% with alpha 0.05. We have improved upon the experimental design in Alekseichuk et al 2017 by personalizing our stimulation frequencies to target the frequencies of peak phase-amplitude coupling during the task. With this methodological improvement, we expect our effect size to increase to 0.6 (see Romei et al. 2016). With this effect size, our sample size has power greater than 85%.

# 13 DATA HANDLING AND RECORD KEEPING

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

## 13.1 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.

## 13.2 CONFIDENTIALITY

Data will be stored in a password-protected cloud-based data system that meets UNC IT Data Security requirements at the level determined by the IRB. 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. Source documents (i.e. paper forms) will be kept in a locked file cabinet in a locked office. The key linking dummy identifiers with participant information will be securely located separate from all other data collected, and will never appear in an electronic format.

### 13.2.1 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.

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 4109).

### 13.2.2 SENSITIVE INFORMATION

Sensitive information may be collected during the screening process in order to determine eligibility (medical history, recreational drug use, etc.). Such information will be de-identified and stored in a secure, locked file cabinet, and will not be used in any further proceedings in the study.

### 13.2.3 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.

## 13.3 SOURCE DOCUMENTS

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

**UNC HUMAN RESEARCH COMMITTEE (IRB).**

- All IRB correspondences are documented
- The study staff is IRB approved prior to performing any study procedures
- Adverse events and deviations are reported to the IRB per current guidelines and stored appropriately
- 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 F) 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 F) are made for missing or incomplete data and to explain any discrepancies or additional comments.

**DNA.**

- Participant names will not be on any of the samples collected. DNA is sequenced to check for one nucleotide. When testing is performed, only de-identified information is shared with an outside party. This information will not be shared with anyone outside of the study personnel, including the participant.

**Hormone Levels**

- Participant names will not be on any of the samples collected. Saliva is collected to assess for sex hormones estradiol, progesterone and testosterone. When testing is performed, only de-identified

information is shared with an outside party. This information will not be shared with anyone outside of the study personnel, including the participant.

## 13.4 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, and CRF entries. The study coordinator will be responsible for AE/SAE documentation and reporting, while the PI will be responsible for the AE assessment, review of the AE documentation forms, and overview of the research staff.

## 13.5 DATA CAPTURE METHODS

Data will be entered directly from the source documents and stored on a password-protected computer in the Frohlich Lab by a researcher. All stored data will be de-identified and will not contain any reference to participant name or other personal information, such as email or phone number.

## 13.6 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.

## 13.7 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.

# 14 ETHICAL CONSIDERATIONS

## 14.1 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).

## 14.2 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.

## 14.3 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 and possible benefits of tACS 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 treatment or 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.

The researcher and potential participants will review the clinical trial in its entirety by reviewing the consent form together in a private location. If the participant is unclear on any part of the consent form, the research will return

to the section and explain further. Participants must sign the informed consent document prior to any procedures taking place. 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.

## 14.4 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. Female participants will be asked if there is any reason to believe they might be 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 transcranial current stimulation studies. All women of child-bearing potential will be asked to take a pregnancy test during the initial session in order to determine eligibility for the study.

## 14.5 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.

## 14.6 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.

# 15 PUBLICATION POLICY

This study will be registered on clinicaltrials.gov once IRB approved. There are no restrictions on publications since this is an investigator-initiated study. The aim is to publish the results of this study in a peer-reviewed, highly-ranked neuroscience journal.

# 16 LITERATURE REFERENCES

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## APPENDIX A: SCHEDULE OF EVENTS

| **Procedures** | Phone Screening | Session 1 | Sessions 2,3,4 with Stimulation |
|---|---|---|---|
| Provide Verbal Consent | x | | |
| Signed Consent Form | | x | |
| Assessment of Eligibility Criteria | x | x | |
| Urine Pregnancy Test | | x | |
| Urine Drug Test | | x | |
| Baseline Assessments (BIS/BAS, Handedness, STAI, PSQI, BDI,P ANAS) | | x | |
| Saliva Collection | | x | |
| Baseline EEG (Resting state) | | x | x |
| Task EEG (Cognitive task with intermittent resting-state) | | x | x |
| Stimulation during task | | | x |
| Stimulation Questionnaire | | | x |

## APPENDIX B: AE REPORT FORM

**Adverse Effects Report:**

*Reasons for Report (adverse event, time, date and place of occurrence if available)*:

1. What do we already know about the study intervention?
    a.
2. What is the temporal relationship of the AE to the study intervention?
    a.
3. Does the AE improve or disappear when the study intervention is stopped?
    a.
4. Is the AE a worsening of baseline symptom(s)?
    a.
5. Is the AE a result of an underlying concurrent medical condition(s) or concurrent medication(s)?
    a.
6. Additional Information provided by research team
    a.

Research team member signature _____

Date_____

Co-Investigator:

_____

_____

_____

_____

_____

_____

Steps to be taken (if applicable)

_____

_____

_____

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_____

Co-I signature

_____Date_____

PI Comments:

_____

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Steps to be taken (if applicable)

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PI signature

_____Date_____

## APPENDIX C: 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 | | | | | | | |
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## APPENDIX D: AE REPORT FORM

| **Participant ID** | **√ if AE meets definition of serious*** | **Grade/Intensity**<br>1. Asymptomatic<br>2. Mild<br>3. Moderate<br>4. Severe | **Date of Incident** | **Relationship to study device**<br>1. Related<br>2. Possibly<br>3. Not Likely<br>4. Not Related | **Was Action Taken?** | **Action(s) Taken:** | **Outcome:**<br>**1. Recovered**<br>**2. Not Recovered**<br>**3. Recovered w/Sequel**<br>**4. Fatal**<br>**5. Unknown** | **PI Initials / Date** |
|---|---|---|---|---|---|---|---|---|
| | | | | | Yes / No | | | |
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| | | | | | Yes / No | | | |
| | | | | | Yes / No | | | |
| | | | | | Yes / No | | | |

Abbreviated Study Title: _____

Participant Name: _____ Date of Birth: _____

Please **INITIAL** next to **"Yes" or "No"** by each line as appropriate **(if "No," an explanation MUST be provided in the notes section below).**

| | | |
|---|---|---|
| _____Yes | _____No | Participant was given a copy of the consent document to read. |
| _____Yes | _____No | Ample time was provided for reading the consent document, and the participant was encouraged to ask questions. |
| _____Yes | _____No | All questions and concerns were addressed to the satisfaction of the participantprior to signing the consent document. |
| _____Yes | _____No | The PI or Sub-I was available for questions prior to the subject signing the consent. |
| _____Yes | _____No | The subject agreed to participate in the study and signed/dated the consent document. |
| _____Yes | _____No | A copy of the signed consent document was provided to the participant |
| | | ❑ Verbal consent for telephone screening was obtained (per IRB approved consent process). Documentation of the process and the individual(s) witnessing the process is described below. |
| _____Yes | _____No | No procedures specifically related to the study other than telephone screening were performed prior to the participant signing the consent document. |

The details of this research study were discussed with the participant, including an explanation of all of the elements of the consent document. The IRB-approved consent document was signed and dated by the participantand a copy of the signed consent document was placed in the participant's medical record (unless otherwise noted). No activities specifically related to the research were initiated until after the execution of the consent document. The principal investigator was notified of the participant's consent to be enrolled in the study and agrees with enrollment of subject.

The participant signed consent document version _____ on

_____*(date)* at _____*(time)*.

Notes:_____

_____

_____

_____

_____

_____

_____

_____ _____ _____

Signature of Person Obtaining Consent Date Time

## APPENDIX F: NOTE TO FILE

IRB#:

PI: Flavio Frohlich

Study Title: [Insert Short Name]

Researcher: _____

Date of Occurrence: _____

Participant ID: _____

Reason for Note:

_____

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Note:

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Corrective action (if applicable):

_____
_____
_____

Signature: _____ Date: _____

## APPENDIX G: TELEPHONE SCRIPT

### Telephone Consent and Screening (2PAC)

Date: _____ SubjectID: _____ Criteria fulfilled: ❒ Yes ❒ No

Hello, my name is _____. I'm calling in regards to your interest in our study on the effects of brain stimulation on brain activity. Do you have about 10 minutes now to hear about the study, answer a few screening questions, and possibly schedule your visit?

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

First, I need to ask for your verbal consent to conduct the screening interview. I will ask questions about your age, medication and drug use, and family and personal health history. You may decline to answer any questions, but please keep in mind that this may affect our ability to determine if you qualify for the study. Of course, the information you provide is strictly confidential, and will not be used for any purpose other than eligibility. Do you consent to participate in the screening interview?

(If 'No', thank them for their time and hang up.)
(If 'Yes', proceed)

Great! This study is looking at how brain activity respond to weak electrical stimulation. In this study, a weak electrical current will be applied to your scalp. Some participants have reported a mild tingling feeling while being stimulated, but no other side effects have been found. It is not a shock and should cause no pain.

This study will include two sessions scheduled a week apart from each other at your convenience, each lasting approximately 3 hours. You will be compensated for your time after each session, with total compensation amounting to $60. We will ask that you maintain a regular sleep schedule during the study, and adhere to restrictions on exercise, caffeine, and alcohol in the day prior to each 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, no, I do not know, or I prefer not to answer. If you are not sure what the question is asking please ask for clarification. You do not need to provide any details in your answer.

---

Age:_____ Sex:_____

---

| | | |
|---|---|---|
| 1. Have you ever had a serious illness/accident that required hospitalization? Are you currently receiving any medical treatment? ..... ..... ..... | ❒ No | ❒ Yes |
| 2. Have you ever had suffered from a brain disease (e.g. epilepsy) or concussion? ..... | ❒ No | ❒ Yes |
| 3. Have you ever been diagnosed with a learning disability or ADD/ADHD? ..... | ❒ No | ❒ Yes |
| 4. Do you suffer from a mental/psychiatric disease, such as depression or schizophrenia? ..... | ❒ No | ❒ Yes |
| 5. Is there any family history of mental/psychiatric diseases? ..... | ❒ No | ❒ Yes |

| | | | |
|---|---|---|---|
| 6. | Do you consume any drugs, such as cannabis? Please note that we will conduct a urine drug test at the first session. ..... | ❒ No | ❒ Yes |
| 7. | Is there any chance that you are pregnant or could become pregnant during the course of the study? (If female) Please note that we will also administer a pregnancy test at the first session. ..... | ❒ No | ❒ Yes |
| **Study obligations** | | | |
| 1. | Do you think you can comply with all the study duties, which include maintaining a regular sleep schedule, and no caffeine, alcohol, or excessive exercise the day before or of a session? | ❒ No | ❒ Yes |

Keeping in mind sessions last about 3 hours, what days and times work best for you?

## APPENDIX H: TRAINING LOG

Title of Training:_____ DATE:_____

By signing below, each staff member verifies they have been trained on the information and understand the obligations/responsibilities associated with this training.

| Training Date (if different than above) | Trainee Name (please print) | Trainee Signature | Training Format (ie Presentation; Self-Study) |
|---|---|---|---|
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Trainer Name (if relevant):_____

Trainer Signature (if relevant):_____