RATIONAL OPTIMIZATION OF TACS FOR TARGETING THALAMO-CORTICAL OSCILLATIONS: SINGLE SESSION IN A DEPRESSIVE EPISODE, EXPERIMENT III

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Co-Investigator:	*Crystal Schiller, PhD; David Rubinow, MD*
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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ANOVA	Analysis of Variance
CFR	Code of Federal Regulations
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
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
Hz	Hertz
IAF	Individualized Alpha Frequency
ICF	Informed Consent Form
LAR	Legally Authorized Representative
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	*Rational optimization of tACS for targeting thalamo-cortical oscillations: Single session in a depressive episode, Experiment III*
Short Title	*SSDE*
Protocol Number	*Version 1.0*
Phase	*Pilot*
Methodology	*Double-blind, randomized, active sham controlled*
Study Duration	*This study will take 18 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 investigate the effects of non-invasive transcranial alternating current stimulation (tACS) on healthy participants and participants with mood disorders.*
Number of Subjects	*80*
Diagnosis and Main Inclusion Criteria	*Eligible participants will be adults between the ages of 18-65 in a current depressive episode OR age and sex-matched health adults with no history of mental or psychiatric illness.*
Description of Intervention (Procedures/methods)	*The participants will be randomized into one of two arms: either 40 minutes of sham tACS or 40 minutes of IAF tACS while in a relaxed, yet experimentally controlled state, by watching a nature movie such as "Reefscape" during stimulation.*
Related IRB Applications	*16-1911*

1 KEY ROLES

1.1 INDIVIDUALS

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1.3 OPTIONAL

IRB

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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
NIH National Institute of Mental Health (NIMH)	N/A	Federal	N/A	N/A	R01MH101547

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

The objective is to use non-invasive electrophysiology to demonstrate that transcranial alternating current stimulation (tACS) indeed modulates human thalamo-cortical alpha oscillations. To achieve translational relevance, we will evaluate the stimulation patterns not only in occipito-parietal cortex, where alpha oscillations are maximal, but also in frontal areas, where altered alpha oscillations correlate with impaired approach motivation. The rationale for this aim is that validation in humans of tACS based on the mechanistic insights on modulation of thalamo-cortical network dynamics will enable and accelerate the further study of optimized tACS in healthy and patient populations.

The study of alpha oscillations (~10 Hz) as a brain stimulation target is significant due to its central role in mediating long-range functional connectivity (von Stein & Sarnthein, 2000), attentional modulation of cortical information processing (Saalmann, Pinsk, Wang, Li, & Kastner, 2012), and disease states such as depression (Leuchter, Hunter, Krantz, & Cook, 2015) and autism (Murias, Webb, Greenson, & Dawson, 2007). Pursuing alpha oscillations is further motivated (1) by other emerging low-intensity stimulation modalities for mood disorders that target alpha oscillations, such as synchronizing transcranial magnetic stimulation (sTMS; Frohlich, 2015; Leuchter, Cook, et al., 2015; Leuchter, Cook, Jin, & Phillips, 2013) and (2) by the observation that the clinically used 10Hz repetitive TMS entrains alpha oscillations (Thut et al., 2011).

Previous tACS studies from other groups have shown that 10Hz tACS is capable to increase alpha oscillations during tACS application and in the post stimulation interval compared to a non-stimulation baseline (Helfrich et al., 2014; Neuling, Rach, & Herrmann, 2013; Vossen, Gross, & Thut, 2015; Zaehle, Rach, & Herrmann, 2010). However, questions of significant importance have remained unanswered. It is unclear to what extent the findings were contaminated by changes in overall state (e.g. drowsy vs. alert) independent of stimulation.We will answer this question by monitoring state by pupillometry. Measurements of pupil diameter in humans index arousal levels that correlate with the activation of the noradrenergic system (Koss, 1986; Murphy, Robertson, Balsters, & O'Connell R, 2011) and power of the alpha oscillation (Hong, Walz, & Sajda, 2014). In addition, alpha tACS studies measuring EEG had rather small sample sizes (12-30 participants). Experiment 1 aims at validating the effect of alpha tACS and its state dependence in a bigger dataset of healthy participants using comparable electrode locations (over occipital regions). Furthermore, we use for the first time a high density EEG (128 electrodes) that will allow to explore the spatial distribution of the effect of alpha tACS.

Experiment 1 serves us to understand how the state might affect the interaction between tACS and alpha oscillations by targeting the alpha oscillation that is correlated with state (arousal/drowsiness). However, several studies have shown that frontal alpha oscillation properties (strength, distribution etc) reflect cognitive processing and impairments in frontal alpha are implicated in psychiatric disorders (Klimesch 2012, Allen and Reznik 2015). Hence, we target the frontal alpha oscillations in Experiments 2 and 3.

Despite behavioral effects of frontal alpha-tACS, it is unclear if target engagement for frontal alpha oscillations follows the same principles. In addition, it remains untested if tACS also engages pathologically altered alpha oscillations. Considering that patients with reduced approach motivation, such as depression, show altered frontal alpha power topographies (e.g. asymmetry) answering these questions is of fundamental importance (Debener et al., 2000). Our second experiment using stimulation electrodes over the frontal cortex in patients with decrease in approach motivation will directly address these questions.

On purpose, we refrain from using the clinical diagnosis of major depressive disorder but rather (following the RDoC principles; Craske 2012) cast a wider net to capture a more complete set of patients that are likely to have altered alpha oscillations. Changes in the symmetry between alpha power in the left and the right hemisphere have been reported to be correlated with a decrease in approach motivation as measured by the BAS scale (de Pascalis et al. 2013), which corresponds to a construct in the RDoC domain of positive valence. In addition, patients with depresssion (MDD and Bipolar depression) often rate higher in the BIS scale compared to healthy individuals (Kasch et al. 2002, Johnson et al. 2003). In this study, we aim to study the effect of transcranial alternating current stimulation on the alpha oscillation in healthy individuals as well as patients who show altered alpha dynamics.

2.2 INVESTIGATIONAL AGENT

Transcranial Alternating Current Stimulation (tACS) is one method that has been demonstrated to enhance alpha oscillations in healthy participants by applying weak electrical currents to the scalp to modulate rhythmic brain activity patterns (Lustenberger et al, 2015).

2.3 DOSE RATIONALE

Stimulation intensity and duration is based on the completed first experiment under this protocol.

2.4 STUDY AIMS/HYPOTHESES

Central Hypothesis: Non-invasive brain stimulation that enhances alpha oscillation increases endogenous alpha power and reduces frontal alpha asymmetry when present.

Aim 1: Our first objective is to study the effect of tACS in healthy humans on neurophysiology measured using hdEEG

Aim 2: Our third objective is to study the effect of tACS on neurophysiology in patients with mood disorders and impaired alpha oscillations and compare it to the effect in healthy humans

3 SUBJECT SELECTION AND WITHDRAWAL

A total of 80 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 one of the following sets of criteria:

Inclusion Criteria for individuals with depressed mood

- Ages 18-65 years
- Hamilton Depression Rating Scale score >8
- Capacity to understand all relevant risks and potential benefits of the study (informed consent)
- Low suicide risk which will be determined through the use of both the Structured Clinical Interview for the DSM-5 and by scoring less than 3 (0,1, or 2) in the Hamilton rating depression scale.
- Negative pregnancy test for female participants

Inclusion Criteria for healthy controls

- Ages 18-65 years
- Hamilton Depression Rating Scale score <8
- Capacity to understand all relevant risks and potential benefits of the study (informed consent)
- Negative pregnancy test for female participants

3.2 EXCLUSION CRITERIA

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

Exclusion Criteria for individuals with depressed mood

- DSM-5 diagnosis of alcohol use disorder within the last 12 months
- DSM-5 diagnosis of substance dependence (other than nicotine) within the last 12 months
- DSM-5 diagnosis of substance abuse (other than nicotine or marijuana) within the last 12 months
- Eating disorder (current or within the past 3 months)
- 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
- Neurological disorders, including but not limited to history of seizures (except childhood febrile seizures and ECT induced seizures), dementia, history of stroke, Parkinson's disease, multiple sclerosis, cerebral aneurism.
- Medical or neurological illness (unstable cardiac disease, AIDS, malignancy, liver or renal impairment) or treatment for a medical disorder that could interfere with study participation
- History of traumatic brain injury, reoccurring seizures or later cognitive rehabilitation or causing cognitive sequellae
- Prior brain surgery
- Any brain devices/implants, including cochlear implants and aneurysm clips
- Co-morbid neurological condition (i.e. seizure disorder, brain tumor)
- Use of illicit drugs, confirmed by a drug test
- Non-English speakers
- Pregnant or nursing females

- Current use of benzodiazepines or anti-epileptic drugs

Exclusion Criteria for healthy controls

- History of major neurological or psychiatric illness, including epilepsy
- Medication use associated with neurological or psychiatric illnesses
- Currently undergoing counseling or psychotherapy treatment for depression, anxiety, eating disorders, PTSD or other behavioral conditions
- First degree relative (parent, sibling, child) with major neurological or psychiatric illness
- Prior brain surgery
- Major head injury
- Any brain devices/implants (including cochlear implants and aneurysm clips)
- Use of illicit drugs, confirmed by a drug test
- Braids or other hair styling that prevents direct access to the scalp (if removal not possible)
- Skin allergies or very sensitive skin
- Non English speakers
- Pregnant or nursing females

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.

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 tDCS/tACS studies. We will verify pregnancy status via a urine pregnancy test for all female participants prior to receiving treatment on Day 1 of Stimulation.

3.3 STRATEGIES FOR RECRUITMENT AND RETENTION

3.3.1 RECRUITMENT

Subjects at this time will be recruited by Jointheconquest.com, a mass email distributed through the UNC service, an email sent to previously interested participants in Dr. Schiller's lab, and flyers posted at locations on campus. We have also created a social media advertisement for Facebook. We believe this multimodal approach will allow us to reach the projected number of participants.

3.3.2 RETENTION

Subjects only complete a single session of the experiment. Therefore, retention is of minimal risk. When collecting data, we are mindful of the time commitment for the participant and ensure that all data is collected and procedures are carried out in a time efficient manner.

4 BASIC STUDY DESIGN

The design for this study is a pilot, randomized, double-blind, sham-controlled, clinical trial which will be used to demonstrate feasibility and collect effectiveness data for further refinement of a tACS approach and for the subsequent design of a follow-up, multi-site, large scale study. We are seeking 80 healthy participants, both male and female, between the ages of 18-65 who belong to one of two cohorts: those experiencing a depressive episode or age and sex-matched health controls. 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.

This is a double-blind, randomized crossover study. We estimate 18 months to complete study enrollment.

Participants will be randomly assigned to one of 2 arms.

Figure 1.

Active sham treatment will include 10 seconds of ramp-in to 1 minute of 10 Hz tACS and a ramp-out of 10 seconds, for a total of 80 seconds of stimulation. The choice of an active sham is motivated to enhance success of patient blinding by mimicking skin sensations associated with tACS. The verum condition will have a 10 second ramp-in and ramp-out with 40 minutes of stimulation for a total of 2420 seconds of stimulation. Stimulation waveform is a sine-wave with 2mA amplitude. In both arms, participants will stay in a relaxed yet controlled state by watching a nature movie ("Reefscape") during stimulation.

Eligible participants will have a single visit approximately 4 hours. All time estimates take into consideration breaks and time variance in administration.

4.1 TREATMENT ASSIGNMENT PROCEDURES

Participants will be randomized into one of 2 arms (*see Figure 1 above*). 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

Charles Zhou will randomize a series of 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 or tACS at IAF) at each session, and will be used with the XSCITE 100 stimulator. An unblinded code sheet that matches these stimulation codes to treatment arm will be kept by Charles Zhou and will not be available to the study coordinator or research assistants.

The unblinded code sheet will have the following information:

1. The initial identifier codes for all potential participants
2. Stimulation code: 6-digit numerical code for the stimulation session
3. Condition number: Numerical code for the condition
4. 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.

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, data from the screening will be retained.

Prior to attending the session, each participant will complete a screening questionnaire (online or phone) to determine preliminary eligibility. This will also include some online assessments (Structured Clinical Interview for the DSM-5 Personality Disorders Screening, as well as the Childhood Trauma Questionnaire, State-Trait Anxiety Inventory (STAI) – Trait, Rumination Scale, BIS/BAS, and Demographics). Participants are not required to fill in these prior to the initial session, but completing these assessments may reduce the duration of their session. Participants will provide verbal consent through the phone screening prior to completing these assessments.

5.2 STUDY VISITS

All participants will undergo a single study visit with the same procedure; the only change will be the stimulation condition.

5.4.1 STUDY VISIT

At the beginning of the session, the participants will be guided through the informed consent and asked to sign the form. Once the consent has been signed, all female participants will be asked to take a Urine Pregnancy Test in order to determine eligibility. All participants will also take a urine drug test to determine eligibility as well.

The session will begin with the Mini International Neuropsychiatric Interview (MINI) and the Hamilton Depression Rating Scale (HDRS). **Both of these assessments will determine suicide risk - if the participant's responses indicate a high risk of suicide (e.g., current plans, 3 or 4 on the suicide item on the HDRS), Dr. Crystal Schiller will be contacted for a brief assessment and to determine the next actions to be taken (if necessary).** Following these assessments, the participant will complete the Temporal Experience of Pleasure Scale (TEPS), the Snaith-Hamilton Pleasure Scale - Clinician Administered (SHAPS-C) and and the Beck Depression Inventory (BDI) prior to the stimulation. Treatment resistance will be assessed using the Maudsley Staging Method by the study coordinator. Breaks will be provided when needed. The participant will also provide a saliva sample that will be used to genotype a single polymorphism called brain derived neurotropic factor (BDNF). These assessments will be administered prior to stimulation in order to determine participant eligibility, with the MINI being used as a diagnostic tool. In total, the assessments should take approximately 1 hour to complete. If the participant is not deemed eligible, they will be compensated for their time and the visit will end. If the participant is deemed eligible, the study visit will proceed as follows.

A study coordinator will apply the stimulation and EEG electrodes to the participant’s scalp. Participants will complete a 2-minute eyes closed resting state EEG recording. Participants will complete an EEG reward-processing task. Participants will be told that the better they are at this task, the more money they will earn as a "bonus". This task is visual, with participants responding to stimuli with button clicks and is expected to last about 25 minutes. Participants will then complete an emotional response EEG task,

which includes pictures. We anticipate this to last approximately 6 minutes. Pre-stimulation resting state EEG will be collected for 5 minutes with eyes open. Participants will respond to the STAI-State, the state complacency scale, and the positive and negative affect schedule (PANAS) following this. Stimulation (tACS or sham tACS) will then be applied for 40 minutes. Post-stimulation resting state EEG with eyes open will be collected for 5 minutes Participants will then respond to the STAI-State, State complacency scale, the PANAS, and the Stimulation Side Effects Questionnaire. To assess any possible change in the emotional response EEG task, it will be repeated. Finally, all equipment will be removed and participants will be compensated.

5.4.3 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 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).
C. 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).
D. Repetitive Thinking Questionnaire (RTQ) is a 22-item self-report assessment using a 4-level Likert scale to assess the frequency of repetitive negative thinking and rumination. This questionnaire has been used to assess traits of worrying about past events with transdiagnostic relevance.
E. Childhood Trauma Questionnaire (CTQ) is a 28-item self-report assessment using a 5-level Likert scale to assess a history of childhood sexual, emotional, and physical abuse or neglect.
F. State Complacency Scale (SCS) is a 19-item self-report assessment using a continuous analog scale to assess satisfaction with the current mood and difficulty changing mood.

6.2 SPECIAL ASSAYS OR PROCEDURES

Each participant will receive one session of stimulation, either with an active sham condition or tACS at IAF. For more information on the stimulation procedures, see section *7.2 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.
B. A study coordinator will be present at all times to ensure safety.

6.4 LABORATORY EVALUATIONS

6.4.1 SCREENING LABORATORY EVALUATIONS

A urine pregnancy test will be performed for any female participant who is of child-bearing potential. All participants will also undergo a urine drug test.

INSTRUCTIONS FOR SPECIMEN PREPARATION, HANDLING, AND STORAGE. For this laboratory evaluation, 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.

6.4.3 SALIVA SAMPLES

We will be collecting a saliva sample 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. We will perform exploratory analyses in which we group participants by BDNF status.

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 until the completion of data collection.

7 STUDY INVESTIGATIONAL PRODUCT

7.1 DEVICE DESCRIPTION

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:

1. Android tablet with user interface application (i.e., App)
2. Stimulator with:
    a. Microprocessor
    b. Function generator chip
    c. Voltage controlled current source
    d. 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.

7.2 SAFETY FEATURES

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.

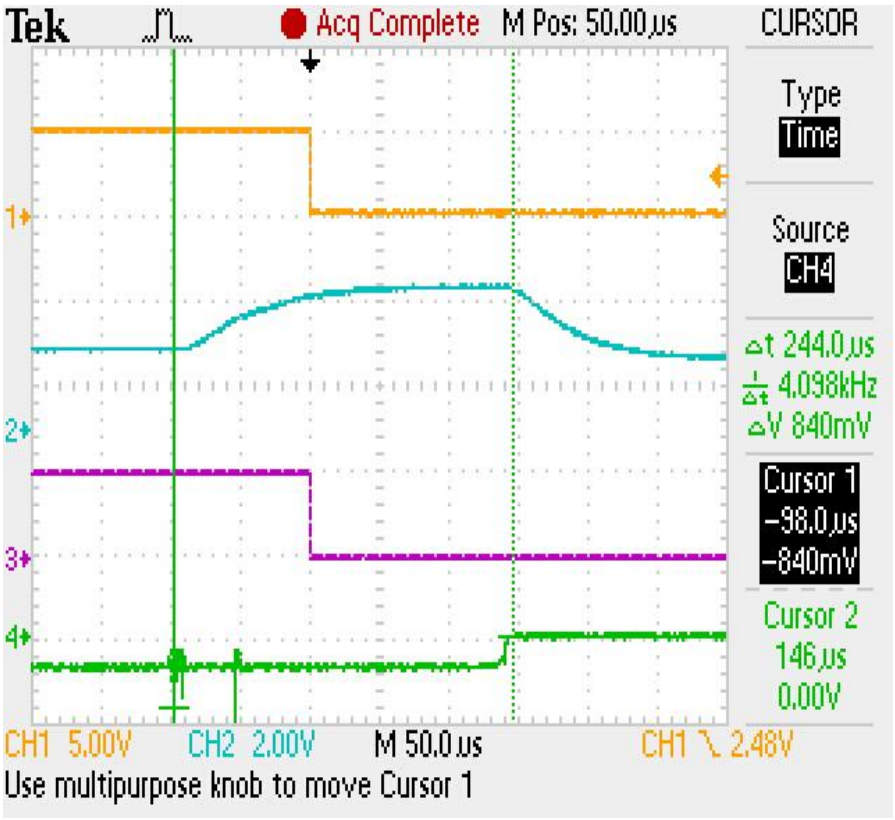
The device is equipped with 4 different stages of safety precautions, all of which protect the participant from high currents. The stages are as follows:

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.

7.3 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 by watching a nature movie. One session of stimulation will be performed per visit for 40 minutes. During the 10 Hz tACS

condition, participants will have a 10 second ramp in and ramp out with 40 minutes of stimulation for a total of 2420 seconds. Stimulation waveforms are sine-waves with a peak-to-peak amplitude of 2 mA. The sham stimulation will include 10 seconds of ramp in to 1 minute of 10 Hz tACS with a ramp out of 10 seconds for a total of 100 seconds of stimulation. Electrodes will be saline soaked, 5x5cm and placed over F3 and F4 with a 5x7cm placed over CZ as a return electrode.

Stimulation devices will be preprogrammed and codes will be randomized to one of the two experimental arms. Researchers will enter the participant-specific code into the App that controls the stimulation and monitor participants during the 40 minutes of the stimulation.

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 daily stimulation questionnaire, and Attachment 2 for an example of the endpoint stimulation questionnaire.*

7.4 ASSESSMENT OF PARTICIPANT COMPLIANCE WITH STUDY INVESTIGATIONAL PRODUCT

Compliance for this study includes attendance of the study visit. Individuals who miss the session and are unable to reschedule will be dropped from the study.

8 POTENTIAL RISKS AND BENEFITS

8.1 BENEFITS TO SUBJECTS AND SOCIETY

Our novel approach introduces non-invasive brain stimulation for mental illnesses and has the potential to treat symptoms in mood disorders. Furthermore, we will enhance the understanding of cortical network dynamics through addressing the role of modulating alpha oscillations with brain stimulation to improve symptoms in patients with mood disorders.

This study is not designed to benefit the individual participants. However, participants in this study may experience some degree of relief from mood symptoms as a result of tACS treatment.

8.2 POTENTIAL RISKS

8.2.1 PSYCHOLOGICAL

Emotional Distress: We will show some images in the emotional memory task that participants might find objectionable, including sexually explicit and violent images that may be difficult to look at. Importantly, these images have been extensively used in several thousand participants in other studies and have been rated (e.g., Affective Picture System Scale (Lang et al., 1999), Nencki Affective Picture Scale (Wierba et al., 2015; Riegel et al., 2015; Marchewka et al., 2015). We will do the following points to minimize the risk:

(1) Each image is only shown for a very short time period (1 second).
(2) We will provide the following information in the consent form, stressing that the participant may withdraw at any time for any reason:

If you decide to take part in this study, you will be asked to view a variety of pictures that have been categorized to be pleasant, neutral, or unpleasant. If any of the media presented should make you feel too uncomfortable to continue with the study, you are free to immediately withdraw your participation and leave without giving up payment. The content of the pictures may include images considered objectionable, such as sexually explicit and violent images that may be difficult to view, which could cause emotional distress. Importantly, these images have been used extensively in several thousand participants in other studies and have been standardized by other study groups and belong to a validated picture system (exemplary standardized systems used are: Affective Picture System Scale or Nencki Affective Picture Scale). We will do the following to minimize risk:
(1) The images are only shown for 1 second
(2) The task can be aborted early if you feel too uncomfortable during it
(3) If you experience any discomfort or concerns after viewing the images, please inform the study coordinator, who can contact the clinician associated with this trial if necessary.

All personnel associated with this study and who might be exposed to the images along with some example pictures. If any personnel feels too uncomfortable, they will not assist during the task and/or administer the task.

Embarrassment: Self-report assessments contain questions regarding sensitive personal information. This risk is necessary in order to assess mood symptoms and associated psychopathology. Subjects will be assured upon intake that only study personnel will see any rating form responses.

8.2.2 PHYSICAL

Risk of Injury and Discomfort: Transcranial current stimulation has been used without any reports of serious side-effects. Therefore, transcranial current stimulation represent an extremely safe and non-invasive therapeutic approach. Passing weak electric current through the scalp is also routinely done for measuring electrode resistance in all EEG recordings. **Importantly, this stimulation mode 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 produce super-threshold activation of neurons** (Frohlich and McCormick, 2010).

Some subjects report a transient mild tingling, burning, or itching underneath the electrodes and headache, but no other side effects have been noted. There is also a rare/theoretical likelihood that stimulation of neuronal circuits can lead to epileptic discharges. To minimize this occurrence, we screen and exclude patients with personal and family history of neurological conditions from the study. During stimulation, the research assistant will ask the subject about his/her comfort level. If the subject reports any pain, stimulation will immediately be stopped.

8.3 REFERRALS FOR MEDICAL FOLLOW-UP OR PSYCHOLOGICAL COUNSELING

We have no indication that our treatment paradigms will in any way increase suicide risk. Patients with high suicide risk will not be included in this study. If an enrolled patient shows signs of suicide risks that were not apparent during enrollment, a referral to a UNC Psychiatry clinician will be required.

After obtaining participant informed consent, the Hamilton Depression Rating Scale (HDRS) will be administered, which contains a question related to suicidal thoughts/actions. If someone answers greater than 2 (i.e., either "suicidal ideas or gesture" or "attempts at suicide"), their participation in the study will be immediately stopped and Dr. Fryml will be contacted for acute assessment. In the case that they do not see anyone for their depression, Dr. Fryml will assist the participant in seeking medical care.

This may include facilitating contact with the subject's psychiatrist/primary care physician in order to establish a plan for safety, continued care, and follow-up. If the patient does not have an established provider, Dr. Fryml will assist the patient in establishing care. If at any point in the assessment, the patient is deemed to be an imminent risk of harm to self or others, study personnel will enlist the aid of campus security to ensure that the patient is safely escorted to the Emergency Department for further care.

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. 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. The medical monitor will be contacted based on the reported intensity on the Adverse Events Questionnaire and the participant's verbal confirmation of intensity.

8.3.1 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.

9 DATA AND SAFETY MONITORING

9.1 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 inform 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.

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.

9.2 SAFETY OVERSIGHT

Safety oversight will be under the direction of the medical monitor, who will review AEs in real time and make decisions regarding a participant's continuation of the clinical trial. The PI will review AEs weekly with research team and may request additional review on a case-by-case basis. The medical monitor will also be present in order to discuss/explain any event(s) that may occur.

9.3 EARLY WITHDRAWAL OF PARTICIPANTS

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

9.3.2 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.

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 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).

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

10.1 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.

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

10.2.1 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-Is, 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-Is), 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 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 and Co-Is will together 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.

10.2.1 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.

10.2.2 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.

10.3 REPORTING PROCEDURES

We will be adopting the following table for reporting procedures:

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 **24 hours** of initial receipt of information	Investigator	Local/internal IRBs
Non-fatal, non-life threatening unexpected, suspected serious adverse reactions	Within **48 hours** of initial receipt of information	Study Coordinator	Local/internal IRBs/Institutional Officials, DSMB
Unanticipated adverse device effects	Within **10 working days** of investigator first learning of effect	Investigator	Local/internal IRBs
Unanticipated problem that is not an SAE	Within **7 days** of the investigator becoming aware of the problem	Investigator	Local/internal IRBs/Institutional officials
All Unanticipated Problems	Within **30 days** of the IRB's receipt of the report of the UP from the investigator	IRB	OHRP
		Investigator	External IRBs

10.3.1 REPORTING OF PREGNANCY

Pregnancy tests will be administered on Day 1 of Stimulation to all women of child-bearing potential. There are no studies that suggest tACS would interfere with pregnancy. However, should a participant become pregnant during the study, their participation will be immediately terminated and will be sent to consult with the Co-I and medical monitor.

10.4 TYPES AND DURATION OF FOLLOW-UP OF PARTICIPANTS AFTER ADVERSE EVENTS

Medical monitors and Co-Is will follow up with participants within one week of an AE.

11 STATISTICAL PLAN

The statistician for this study is Dr. Flavio Frohlich.

11.1 STATISTICAL ANALYSIS STRATEGIES

The analysis will rely on a repeated-measures ANOVA model for the paired response [S_{after}, S_{before}] conditional on cohort (mood disorder vs healthy). We will test the null hypothesis that "The mean difference ($S_{diff} = S_{after}-S_{before}$) in both subpopulations is exactly zero." The expected result is that the estimated mean difference will be large in both cohorts. We will also test the null hypothesis that "mean $S_{diff[mood\ disorder]}$ is exactly equal to mean $S_{diff[healthy]}$." We anticipate that this test is highly likely to be inconclusive because we believe that (mean $S_{diff[mood\ disorder]}$ - mean $S_{diff[healthy]}$) is near zero or small for the target subpopulations from which we are sampling. We will address the questions "How large is the effect of stimulation in each of the two target subpopulations?" and "How large is the between-subpopulation difference?" Based on studies that we have described above (Neuling et al. 2013), we expect to see large effect sizes for the main effect and small effect sizes for the interaction.

Primary outcomes:

- Interaction in the effect of tACS on left frontal alpha oscillation in the depressed group. Two-way interaction of within-participant factor of before/after tACS and between-participant factor of alpha-tACS/placebo.
- Interaction in the effect of tACS on left frontal alpha oscillation in the healthy group. Two-way interaction of within-participant factor of before/after tACS and between-participant factor of alpha-tACS/placebo.
- Three-way interaction in the effect of tACS on left frontal alpha oscillations between both groups (healthy and patient), session (before and after), and stimulation (alpha-tACS and placebo).

11.2 SAMPLE SIZE DETERMINATION

Number of included participants in this experiment allows us to obtain significance (significance level 0.05) on a mixed measure ANOVA with a power of 80% for effects with a large effect size (f>=0.4). Two ANOVAs will be run, one for each group (healthy and patient): two-way with between-participant factor stimulation (verum and sham) and within-participant factor session (before and after). We expect to see a large effect sizes when assessing the main effect session on alpha power (primary outcome). Alpha power for the 2 sessions will be highly correlated based on previous studies (r-value ~ 0.9)(Mathewson et al., 2015). Thus, we have planned to have at least 40 participants in each ANOVA (40 per group healthy and patient).

11.3 DATA MANAGEMENT

Data will be stored in a password-protected cloud-based data system that does not contain any patient 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

To ensure confidentiality, all data will only be referenced by a dummy identifier. Source documents (i.e. paper forms) will be kept in a locked file cabinet in a locked office. In addition, all data will be de-identified and stored on a password-protected computer. 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.

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-Is 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 4109).

12.2.2 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.

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 clinical trial 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
- 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.

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, 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. The CTRC nurse will serve as the medical monitor for the study.

12.5 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.

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 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.

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. 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.

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

This study will be registered on clinicaltrials.gov once IRB approved. There are no restrictions on publications since this is an investigator-initiated study funded by a grant agency (NARSAD) that has no influence on the publications resulting from this study. The aim is to publish the results of this study in a peer-reviewed, highly-ranked psychiatry journal.

15 LITERATURE REFERENCES

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APPENDIX A: SCHEDULE OF EVENTS

Procedures	Phone Screening	Stimulation Day
Provide Verbal Consent	x	
Signed Consent Form		x
Assessment of Eligibility Criteria	x	x
Urine Pregnancy Test		x
Urine Drug Test		x
Baseline Assessments		x
Saliva Sample		x
EEG during task		x
EEG during rest		x
Stimulation		x
EEG during rest		x
EEG 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 therapy?
    a.
2. What is the temporal relationship of the AE to the study therapy?
    a.
3. Does the AE improve or disappear when the therapy 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)

_____

_____

_____

_____

_____

Co-I signature

_____Date_____

PI Comments:

_____

_____

_____

_____
_____
_____

Steps to be taken (if applicable)

_____
_____
_____
_____
_____

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)
Initials	Reference ID					

APPENDIX D: AE REPORT FORM

Participant ID	**√ if AE meets definition of serious***	**Grade/Intensity** 1. Asymptomatic 2. Mild 3. Moderate 4. Severe	**Date of Incident**	**Relationship to study device** 1. Related 2. Possibly 3. Not Likely 4. Not Related	**Was Action Taken?**	**Action(s) Taken:**	**Outcome** **1. Recover** **2. Not Recov** **3. Recover w/Seque** **4. Fatal** **5. Unknov**
					Yes / No		

Participant ID	**√ if AE meets definition of serious***	**Grade/Intensity** 1. Asymptomatic 2. Mild 3. Moderate 4. Severe	**Date of Incident**	**Relationship to study device** 1. Related 2. Possibly 3. Not Likely 4. Not Related	**Was Action Taken?**	**Action(s) Taken:**	**Outcome** **1. Recover** **2. Not Recov** **3. Recover w/Seque** **4. Fatal** **5. Unknow**
					Yes / No		
					Yes / No		
					Yes / No		
					Yes / No		
					Yes / No		
					Yes / No		
					Yes / No		
					Yes / No		
					Yes / No		

Appendix E: Informed Consent Quiz

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 and/or the participant's legally authorized representative (LAR) was given a copy of the consent document to read.
_____Yes	_____No	Ample time was provided for reading the consent document, and the participant (or participant's LAR) was encouraged to ask questions.
_____Yes	_____No	All questions and concerns were addressed to the satisfaction of the participant (or participant's LAR) prior 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 (or subject's LAR) 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 (or participant's LAR).
		❑ Verbal consent 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 were performed prior to the participant signing the consent document.

The details of this research study were discussed with the participant (or participant's LAR), including an explanation of all of the elements of the consent document. The IRB-approved consent document was signed and dated by the participant (or participant's LAR) and 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 (or participant's LAR) 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:

_____
_____

Note:

_____
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Corrective action (if applicable):

_____
_____
_____

Signature: _____ Date: _____

APPENDIX G: TELEPHONE SCRIPT

Telephone Consent and Screening (16-1911 Experiment 3)

Date: _____ Screening ID: _____ Criteria fulfilled: ❒ Yes ❒ No

Hello, my name is _____. I'm calling in regards to your interest in our study on tACS stimulation. 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 a single session of transcranial alternating current stimulation, or tACS, influences brain activity in patients with depressed mood and in non-patient controls. 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 a single 4 hour session. You will be compensated for your time, regardless if you qualify, with a total possible compensation of $90. 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 the session. We will also administer a urine drug test, and female participants will be required to take a urine pregnancy test. We also administer electroencephalogram or EEG during this visit. Have you heard of EEG before? (*Explain EEG if necessary, clarify, ensure participant understands*). Are you still interested in participating?

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

Great! In order to make sure you are 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, or are you currently being treated for a neurological condition (i.e., epilepsy, migraines)?	❒ No	❒ Yes
2. Are you currently taking medication for the treatment of depression or any other psychiatric illness? What medications are you taking?	❒ No	❒ Yes
3. Are you currently taking any medication for ADD or ADHD?	❒ No	❒ Yes
4. Are you currently diagnosed with a psychiatric illness? (Depression?)	❒ No	❒ Yes
5. Are you currently undergoing counseling or psychotherapy treatment for depression, anxiety, eating disorders, PTSD, or other behavioral conditions?	❒ No	❒ Yes
CONTROL GROUP		
a. Do you have a first degree relative (parent, sibling, or child) with a history of neurological or psychiatric illness?	❒ No	❒ Yes
DEPRESSED GROUP		
a. Have you been diagnosed with a depressive condition by a professional (i.e., a psychiatrist or licensed clinician)?	❒ No	❒ Yes
b. Have you ever been hospitalized?	❒ No	❒ Yes
• If yes, was it related to depression or psychiatric illness?	❒ No	❒ Yes
• If yes, when did this occur? _____		
c. How long have you been depressed? _____		
6. Have you ever had a traumatic brain injury or serious concussion?	❒ No	❒ Yes
7. Have you ever had brain surgery?	❒ No	❒ Yes
8. Do you have any brain devices or implants, including a cochlear implant or aneurysm clip?	❒ No	❒ Yes
9. Do you use any drugs, including cannabis? Please note that we will administer a urine drug 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
2. We will also ask you to fill out a series of questionnaires electronically before your first session. These questionnaires will ask for information about your sleep habits, personality traits, etc. All responses will be deidentified and stored securely in the UNC REDCap system. Would you be comfortable with filling out these questionnaires?	❒ No	❒ Yes

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	(ie Pre

Trainer Name (if relevant):_____

Trainer Signature (if relevant):_____