Augmenting single-session behavioral activation (BA) with delta-beta transcranial alternating current stimulation (tACS) for the treatment of depression

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Master Protocol Document

Title	Augmenting single-session behavioral activation (BA) with delta-beta transcranial alternating current stimulation (tACS) for the treatment of depression
Sub-Title	Augmenting Behavioral Activation with tACS
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Version Number 2	19 SEPTEMBER 2022

I have read, understood, and approved this version of the protocol.

Principal Investigator: ____ _ Date: ____9/19/2022_____

Statistical Co-investigator: _____ Date: ____9/19/2022_____

disclosed in any medium to appropriate investigators, Institutional Review Boards, Scientific Review Committees, and others who are directly involved in the study specified herein under the condition that they keep the information confidential.

Table of Version Changes

Previous Version No.	Affected Sections	Summary of the Changes to the Protocol	Reason for Changes
1 **AUGUST 19 2022**	**1, 2, 3, 4, 5, 7, 8, 9, 12, 13**	**CLARIFIED TIMELINE FOR SESSIONS, REVISED STATISTICAL PLAN, INCLUDED RATIONALE FOR STUDY DESIGN**	**INCORPORATED SRC FEEDBACK.**

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Statement of Compliance

This study will be conducted as specified in the protocol and in accordance with the *International Conference on Harmonisation Guidelines for Good Clinical Practice* (ICH E6) and the *Code of Federal Regulations on the Protection of Human Subjects* (45 CFR Part 46).

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the *Institutional Review Board* (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

If required by the IRB, the master protocol document, informed consent form(s), recruitment materials, and all participant materials will be submitted to the *Scientific Review Committee* (SRC) prior to IRB review (research.unc.edu/clinical-trials/src).

The statistical analysis plans will be consistent with guidance in CONSORT Statement [1] or STROBE Statement [2], ICMJE recommendations [3], the 2016 and 2019 statements of the American Statistical Association [4,5], and recommendations in Nature [6,7].*

All personnel involved in the conduct of this study have completed human subjects protection training.

* [1] www.consort-statement.org
[2] www.strobe-statement.org
[3] www.icmje.org
[4] Wasserstein RL, et al. (2016), The ASA's Statement on p-Values, ***The American Statistician***, 70:2, 129-133
[5] Wasserstein RL, et al. (2019), Moving to a World Beyond p < 0.05, ***The American Statistician***, 73:sup1, 1-19
[6] Amrhein, et al. (2019) Scientists rise up against statistical significance, ***Nature*** 567, 305-307
[7] Editorial (2019) It's time to talk about ditching statistical significance: Looking beyond a much used and abused measure would make science harder, but better. ***Nature*** 567, 283-283.

Table of Abbreviations

AE / SAE	adverse event / serious adverse event
ANOVA	analysis of variance
BA	Behavioral activation
BADS	Behavioral Activation for Depression Scale
BIS/BAS	Behavioral Inhibition System / Behavioral Activation System questionnaire
CFR	U.S. Code of Federal Regulations (www.eCFR.gov)
CT.gov	ClinicalTrials.gov website
C-SSRS	Columbia Suicide Severity Rating Scale
DSMB	data and safety monitoring board
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th Edition)
ECT	Electroconvulsive therapy
EEG	Electroencephalography
FDA	U.S. Food and Drug Administration (www.fda.gov)
GCP	good clinical practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GLMM	Generalized linear mixed model
GVS	galvanic vestibular stimulation
HDRS	Hamilton Depression Rating Scale
HIPAA	U.S. Health Insurance Portability and Accountability Act (www.hhs.gov/hipaa)
ICH	International Council for Harmonization (www.ich.org)
ICMJE	International Committee of Medical Journal Editors (www.icmje.org)
IDAS	Inventory of Depression and Anxiety Symptoms
IRB	institutional review board
MDD	Major depressive disorder
MDE	Major depressive episode
MINI	Mini International Neuropsychiatric Interview
MPD	master protocol document
N	number of enrolled participants
OCT	UNC Office of Clinical Trials (research.unc.edu/clinical-trials)
OHRP	Office for Human Research Protections
PHI	protected health information
PI	principal investigator
RCT	randomized controlled trial
REDCap	Research Electronic Data Capture system
RRS	Rumination Response Scale
SD	standard deviation
SE	standard error
S-EEfRT	Streamlined Effort Expenditure for Rewards Task
SHAPS	Snaith Hamilton Pleasure Scale – Self-Report
SHAPS-C	Snaith Hamilton Pleasure Scale – Clinician Administered
SOP	standard operating procedures
SRC	UNC Scientific Review Committee (research.unc.edu/clinical-trials/src)
STAI	State-Trait Anxiety Inventory
tACS	Transcranial alternating current stimulation
tDCS	Transcranial direct current stimulation
TEPS	Temporal Experience of Pleasure Scale
TMS	Transcranial magnetic stimulation
TraCS	N.C. Translational and Clinical Sciences Institute (tracs.unc.edu)
tRNS	transcranial random noise stimulation
UNC	The University of North Carolina

1. Protocol Synopsis

Title	Augmenting single-session behavioral activation (BA) with delta-beta transcranial alternating current stimulation (tACS) for the treatment of depression
Study Description	The purpose of this study is to examine whether concurrent transcranial alternating current stimulation (tACS) augments the effects of a single session behavioral activation (BA) treatment of depression. Following a series of clinical assessments, participants will perform a reward-based decision-making task while electroencephalography (EEG) is collected. Then, all participants will take part in a single-session 90-minute BA intervention; half of the participants will receive delta-beta tACS during the final 30 minutes of the session and half will receive an active sham stimulation. Participants will return two weeks later for another task-based EEG. Four weeks after the intervention session, they will receive self-report questionnaires via email to complete online.
Specific Aims **(objectives)**	**Aim 1 (PRIMARY).** Evaluate the effects of delta-beta transcranial alternating current stimulation (tACS) on depression symptom severity from pre- to post-treatment. **Aim 2 (SECONDARY).** Examine changes in goal-directed behavior during a reward-based decision-making task from pre- to post-treatment. **Aim 3 (SECONDARY).** Investigate changes in delta-beta coupling during a reward-based decision-making task from pre- to post-treatment. **Aim 4 (EXPLORATORY).** Explore the effects of delta-beta transcranial alternating current stimulation (tACS) on anhedonia symptom severity from pre- to post-treatment.
Target Population	**Inclusion Criteria** We will recruit individuals 18 years and older who meet criteria for current major depressive disorder (MDD) as captured by the Mini International Neuropsychiatric Interview (MINI). Participants will be recruited from the Chapel Hill and Durham areas. **Exclusion Criteria** - Participants must not have active suicide intent as determined by the Columbia Suicide Severity Rating Scale (C-SSRS). Active suicide intent will be captured in responses to items 4 and/or 5 on the C-SSRS. - Participants must not meet criteria for current severe substance use disorder, anorexia nervosa, or active psychosis as captured by the MINI. - Participants may not currently be in psychotherapy and have not received any other psychotherapy and/or stimulation (ECT, TMS) within the last 4 weeks.

	- Any participants taking psychotropic medication must be on a stable dose for at least 4 weeks with no planned dose changes within the next 4 weeks. - (for female participants) Participants must not be pregnant or breastfeeding. - Participants may not have any medical or neurological illness for which symptom presentation or treatment could interfere with study participation - Participants may not have undergone prior brain surgery - Participants may not have any brain devices/implants, including cochlear implants and aneurysm clips - Participants may not have had brain injury or concussion within the last three months - Participants may not have a history of brain injury requiring current treatment
Numbers of Enrollees	Our target sample size is N = 40. 20 participants will be assigned to the BA + delta-beta tACS condition and 20 will be assigned to the BA + active sham condition. We conservatively estimate to enroll 80 participants as a ceiling for the sake of IRB approval. We anticipate that at least n = 30 of the enrollees will complete all aspects of the protocol and have complete data.
Interventions or Exposures/Conditions	Single-session BA: Participants will take part in a 90-minute BA intervention tailored to treat depression. This intervention will include psychoeducation, activity monitoring, evaluation of values, and activity planning and scheduling. Neurostimulation: We will use the DC-STIMULATOR MC Stimulator Plus for investigational purposes to deliver either cross-frequency delta-beta or active sham transcranial alternating current stimulation. Active sham treatment will include 20 seconds of ramp in to 40 seconds of tACS with a ramp out of 20 seconds for a total of 80 seconds of stimulation.
Outcome Measures	**For Aim 1 (PRIMARY).** Change in clinician-rated depressive symptoms using HDRS between baseline visit and 2-week follow-up visit. **For Aim 2 (SECONDARY).** Phase-amplitude coupling between delta-beta oscillations during task performance of the Streamlined Expenditure of Effort for Reward Task (S-EEfRT) at baseline visit and 2-week follow-up visit**.** **For Aim 3 (SECONDARY).** Behavioral metric, percentage of hard trials chosen, during the S-EEfRT at baseline visit and 2-week follow-up visit. **For Aim 4 (EXPLORATORY).** Change in clinician-rated anhedonia symptoms using SHAPS-C between baseline visit and 2-week follow-up visit.

Statistical Analysis Plans for Each Aim	**Aim 1 Plans.** Repeated-measures ANOVA with one within-participant factor (before and after treatment) and one between-participants factor (delta-beta, sham) comparing change in clinician-assessed depressive symptoms. **Aim 2 Plans.** Repeated-measures ANOVA with one within-participant factor (before and after treatment) and one between-participants factor (delta-beta, sham) comparing change in delta-beta coupling. **Aim 3 Plans.** Repeated-measures ANOVA with one within-participant factor (before and after treatment) and one between-participants factor (delta-beta, sham) comparing change in goal-directed behavior. **Aim 4 Plans.** Repeated-measures ANOVA with one within-participant factor (before and after treatment) and one between-participants factor (delta-beta, sham) comparing change in clinician-assessed anhedonia symptoms.
Study Duration	1 year
Participation Duration	Study participation for each participant will be approximately 4 weeks. Completion includes three in-person sessions: a baseline clinical assessment and EEG session, an intervention session, and a follow-up assessment and EEG session two weeks later. The baseline clinical assessment and EEG session will take approximately 3 hours. The intervention session will take approximately 2 hours. The follow-up visit will take approximately 2.5 hours. Participants will be sent questionnaires to complete online 4 weeks after the intervention visit. These questionnaires are expected to take approximately 0.5 hours to complete. We estimate that total participation will take approximately 8 hours.
Enrollment Duration	8 months

2. Introduction

2.1. Background Information

Major depressive disorder (MDD) is a common and debilitating disorder characterized by heterogeneity and variability of treatment response (Fava et al., 1997; Friedrich, 2017). Behavioral activation (BA) is a treatment for MDD and depressive symptoms aimed at increasing engagement with pleasurable and mastery activities in line with an individual's identified values (Dimidjian et al., 2014; Mazzucchelli et al., 2009). Obstacles to treatment engagement, including time and resource limitations, often contribute to worse treatment outcomes and have led to consideration of single-session depression interventions (Gawrysiak et al., 2009; Schleider et al., 2022; Parra et al., 2019; Read et al., 2016 Wasil et al., 2021), and initial studies have largely found reductions in stress and depressive symptoms, as well as increases in self-reported agency following single-session BA interventions.

Additionally, recent findings have emerged that suggest non-invasive brain stimulation may be a particularly effective intervention for treatment-resistance. Guided by prior research from our lab, this study will investigate the effect of delta-beta transcranial alternating current stimulation (tACS) on response to single-session BA for depression. Coupling between low-frequency cognitive control signals in the delta frequency band (1-4 Hz)

emanating from prefrontal cortex and the amplitude of beta oscillations (15-30 Hz) in the primary motor cortex was found to be positively correlated with goal-directed behavior in our previous experiment (Riddle et al., 2022). Furthermore, individual differences in the strength of delta-beta coupling were negatively correlated with depressive symptoms in a sample that included patients within a major depressive episode.

The proposed study will examine whether non-invasive brain stimulation targeted to enhance neural activity related to goal-directed behavior will increase the efficacy of BA in patients with major depressive disorder. This approach was selected based on literature that found reward-related deficits associated with depression (Admon & Pizzagalli, 2015; Grahek et al., 2019) and the proposed mechanisms of action for BA (Nagy et al., 2020). In light of the link between delta-beta coupling and goal-directed behavior (Riddle et al., 2022), delta-beta tACS will be aligned with the timing of the "activity planning and scheduling" phase of BA. Building on the link between specific symptoms of depression (e.g., anhedonia) and reward processing (der-Avakian et al., 2012), exploratory analyses will examine whether treatment may uniquely target anhedonic symptoms.

We believe that the proposed study will provide an important test of novel treatments particularly tailored to depression and the potential role of reward-related pathways. Results may pave the way for larger clinical trials to establish a more personalized treatment approach.

2.2. Scientific Rationale

This study is a randomized, sham-controlled interventional parallel-arm clinical trial. All participants will receive the same single-session BA intervention. Concurrent with the goal-directed phase of the BA intervention, participants will receive either delta-beta tACS or an active sham stimulation. All researchers involved in data collection and the participants receiving stimulation will be blind to the stimulation condition to reduce bias in the data collection process, i.e., double-blinding. A previous study in the lab found that depressed participants demonstrated reduced delta-beta coupling (Riddle et al., Cerebral Cortex 2022), and a study currently ongoing is testing the impact of delta-beta stimulation on performance during a reward-related decision-making task (NCT05084924). Moreover, another previous study recorded EEG during the S-EEfRT in patients with MDD. This study found that participants with MDD demonstrated reduced goal-directed behavior and reduced delta-beta coupling. This preliminary data provides strong evidence that stimulation delivered in a delta-beta pattern should be beneficial to reward-related behavioral outcomes that are the focus of BA. The proposed study will build on these findings to determine whether a BA intervention combined with targeted stimulation may lead to improved treatment outcomes in reward-related constructs.

3. Specific Aims

3.1. Aim 1

(PRIMARY) Evaluate the effects of delta-beta transcranial alternating current stimulation (tACS) on depression symptom severity from pre- to post-treatment.

3.2. Aim 2

(SECONDARY) Examine changes in goal-directed behavior during a reward-based decision-making task from pre- to post-treatment.

3.3. Aim 3

(SECONDARY) Investigate changes in delta-beta coupling during a reward-based decision-making task from pre- to post-treatment.

3.4. Aim

(EXPLORATORY) Explore the effects of delta-beta transcranial alternating current stimulation (tACS) on anhedonia symptom severity from pre- to post-treatment.

Table 1. Examples of Alignment of the Specific Aims with Measures and Aim-Specific Statistical Analysis Plans

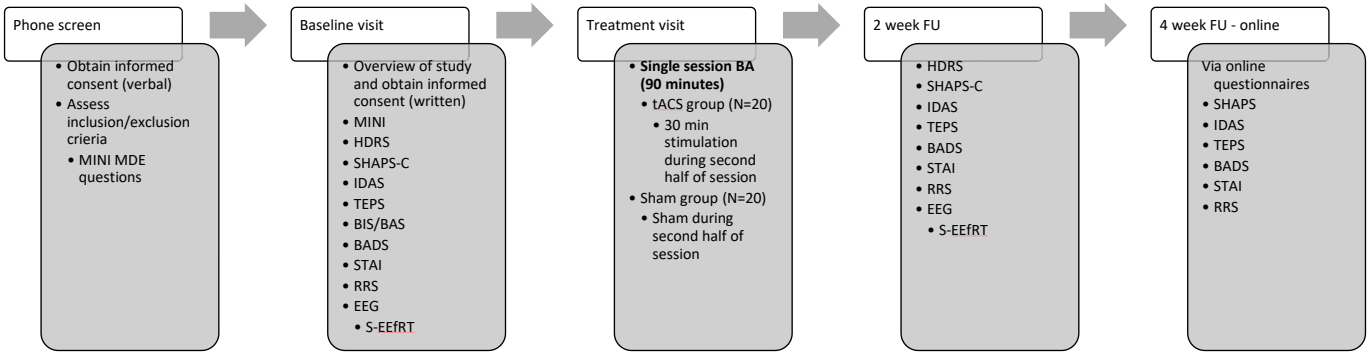
Specific Aim	Outcomes Measures	Population Parameters to be Estimated ("Estimands")	Statistical Estimators
Aim 1. (PRIMARY) Evaluate the effects of delta-beta transcranial alternating current stimulation (tACS) on depression symptom severity from pre- to post-treatment.	Change in clinician-rated depressive symptoms using HDRS between baseline visit and 2-week follow-up visit.	Treatment response	ANOVA
Aim 2. (SECONDARY) Examine changes in goal-directed behavior during a reward-based decision-making task from pre- to post-treatment..	Phase-amplitude coupling between delta-beta oscillations during task performance of the Streamlined Expenditure of Effort for Reward Task (S-EEfRT) at baseline visit and 2-week follow-up visit.	Treatment response	ANOVA
Aim 3. (SECONDARY) Investigate changes in delta-beta coupling during a reward-based decision-	Behavioral metric, percentage of hard trials chosen, during the S-EEfRT at baseline visit and 2-week follow-up visit.	Treatment response	ANOVA

making task from pre- to post-treatment.			
Aim 4. (EXPLORATORY) Explore the effects of delta-beta transcranial alternating current stimulation (tACS) on anhedonia symptom severity following from pre- to post-treatment.	Change in clinician-rated anhedonia symptoms using SHAPS-C between baseline visit and 2-week follow-up visit.	Treatment response	ANOVA

4. Study Design

This is a single site interventional study evaluating the use of transcranial alternating current stimulation (tACS) to augment a single-session behavioral activation (BA) intervention in the treatment of depressive symptoms (Figure 1). To examine the effects of neurostimulation on treatment response, participants will be randomized to receive either cross-frequency transcranial alternating current stimulation (tACS) or an active sham.

Figure 1. Study schema



Choice of dosage of neurostimulation:

Transcranial alternating current stimulation (tACS) is an extremely safe non-invasive stimulation paradigm without a single serious adverse event directly related to stimulation. The same tACS method has been used during performance of a task with intermittent resting state EEG in our previous approved UNC IRB protocol 18-0003 (NCT03800030) that was overseen by Dr. Riddle. A similar experimental design using a single session with reward-based decision-making tasks and tACS in participants with major depressive disorder (MDD) was approved in our previous UNC IRB protocol 21-1321 (NCT03449979) that was overseen by Dr. Riddle. Transcranial alternating current stimulation (tACS) applies a weak electric current to the scalp and all previous studies (approximately 15 to date) performed in the Carolina Center for Neurostimulation have received a "non-significant risk designation" from the UNC IRB. Thus, no direct FDA oversight is required and no investigational device application filing is required. Further conversations with the regulatory core of the UNC CTSA and the director of the Office of Human Research Ethics that administers the UNC IRB over the years have consistently confirmed this classification. We will deliver tACS using a delta-beta stimulation waveform that was designed to mimic the endogenous cross-frequency coupling pattern observed by EEG. For the active arm of this RCT, the interventional stimulation will be 30 minutes of tACS delivered during the second phase of BA. For the placebo arm, participants will receive active sham tACS in which delta-beta tACS is delivered for 1 minute and then returns to baseline (approximately 15 second ramp up and ramp down). This active sham is designed to mimic the sensation of receiving stimulation without delivering a sufficient dose of tACS to influence the efficacy of BA. The delta-beta waveform was designed based on our previous experiment that observed delta-beta coupling between prefrontal and motor cortex in a

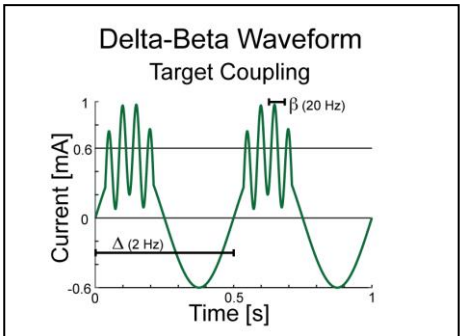


Figure 2. Electrical waveform for delta-beta tACS. Peak stimulation amplitude is 1 mA for target electrodes.

reward-based decision-making task in participants with MDD (Riddle et al., 2022). The timing of the stimulation was chosen to align with the "activity planning and scheduling" portion of BA, when goal-directed behaviors are thought to be maximal. The stimulation amplitude delivered is standard for tACS studies (Ahn, Mellin et al. 2018, Alexander, Alagapan et al. 2019) – stimulation peaks at 1 mA during the peak of the high-frequency component for target electrodes (see Y-axis of Figure 2). The high frequency component consists of 3.5 cycles of a sine-wave of the high frequency that is centered at 90 degrees of each cycle of the low-frequency component. Stimulation peaks at 2 mA zero-to-peak for the return electrode, but the electrode size is 35 cm^2 for the return electrode and 20.25 cm^2 for each of the target electrodes. Thus, the current density is comparable between the two: 0.057 mA/cm^2 for the return electrode and 0.049 mA/cm^2 for the target electrodes. We will use the international 10-20 head measurement system to place the tACS electrodes on the scalp. The two target electrodes will be placed anterior and ventral to F3 and posterior and ventral to C3. The return electrode will be centered on FCz. This electrode montage is designed to deliver synchronized stimulation to the prefrontal cortex and motor cortex to enhance cross-frequency coupling between these brain regions.

4.1.Treatment Design

Participants will take part in a single-session behavioral activation (BA) intervention. This intervention was adapted from standard BA protocols for the treatment of depression to be completed in a single, 90-minute session. This intervention will have 4 main components based on prior protocols:

- Treatment overview and rationale
- Tracking of daily activities
- Exploration of values
- Planning/scheduling activities

Participants will be stimulated with the commercial, CE-certified Neuroconn multiple channel (MC) 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 MC is a CE-certified medical device for conducting non-invasive transcranial direct current stimulation (tDCS) in humans. Direct current 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 MC 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 includes a digital display with various stimulation modes to be selected and stimulation parameters such as current strength, duration, fade-in and fade-out to be set.

DC-STIMULATOR MC features:

- 4 programmable, micro-processor-controlled constant current sources using inependent channels (optional: 16 channels)
- For transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), cranial electrical stimulation (CES), galvanic vestibular stimulation (GVS) and transcranial random noise stimulation (tRNS)
- 4 standard modes - tDCS (continuous stimulation) - pulse (cyclical stimulation activation/deactivation) - sinus (sinus wave) - noise (normally distributed)
- Current strength and curve forms adjustable up to ¬±4,000 ¬µA, AC current strength adjustable up to 8,000 ¬µA (peak-to-peak)
- Frequencies adjustable up to 1,000 Hz, phase freely adjustable

- Various types of stimulation can be selected and combined - continuous stimulation, cyclical switching on and off of stimulation, sinusoidal stimulation
- Medical panel PC for the use and programming of stimulation modes and stimulation sequences

4.2. Experimental Design

All participants will receive the single-session 90-minute BA intervention. Participants will be randomized to either receive either cross-frequency transcranial alternating current stimulation (tACS) or an active sham.

4.3. Measurement Design

Table 2. Variables of interest: their occasions of evaluation, their uses for the aims, their roles in the study

Variables within Domains	Scale[1]	Occasions[2]	Aims[3]	Main Roles
Identifiers				
Participant's unique ID	nominal	all	all	identifier
Treatment Regimen (A or B)	binary	2	all	identifier
Behavioral Measures				
goal-directed behavior (S-EEfRT)	percentage	0, 2	Aim 3	secondary outcome
EEG Measures				
delta-beta coupling (S-EEfRT)	continuous	0, 2	Aim 2	secondary outcome
Clinician Rated Measures				
SHAPS-C	interval	0, 2	Aim 4	exploratory outcome
MINI	categorical	0	--	screening
HDRS	interval	0, 2	Aim 1	primary outcome
Patient-Reported Measures				
SHAPS	interval	3	--	covariate uses
IDAS	interval	0, 2, 3	all	covariate uses
TEPS	interval	0, 2, 3	all	covariate uses
BIS/BAS	interval	0	all	covariate uses
BADS	interval	0, 2, 3	all	covariate uses
RRS	interval	0, 2, 3	all	covariate uses
STAI	interval	0, 2, 3	all	covariate uses
Safety Monitoring				
AEs and SAEs documentation	events	0, 1,2,3	--	safety monitoring

[1] Units of measurement or the scale.
[2] Occasions of evaluation or retrieval: **S** = screening, **0** = baseline visit, **1** = treatment visit, **2** = 2 week FU, **3** = 4 week FU.
[3] The specific aims in which the variable will play a role in data analyses.
[4] Uses: assess medication adherence, mediation analyses, and exploratory analyses

In Table 2, the treatment regimens are:
A = BA + delta-beta tACS,
B = BA + sham stimulation.

5. Study Participants

5.1. Numbers of Participants

5.1.1. Number to be screened: n ≤ 80

5.1.2. Number to be enrolled:

Our target sample size is N = 40. 20 participants will be enrolled in the BA + tACS condition and 20 will be enrolled in the BA + active sham condition. Conservatively, we may enroll up to 80 participants, but a potentially substantially high number of people may not meet criteria for MDD as assessed by the MINI at the baseline visit.

5.2. Eligibility Criteria

Eligibility will be determined based on inclusion and exclusion criteria, defined below.

5.2.1. Inclusion Criteria

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

- Between the ages of 18 and 65
- 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
- DSM-5 diagnosis of major depressive disorder (MDD) as assessed by the MINI

5.2.1. Exclusion Criteria

Any individual who meets one or more of the following criteria will be excluded from participation:

- Participants must not have active suicide intent as determined by the Columbia Suicide Severity Rating Scale (C-SSRS). Active suicide intent will be captured in responses to items 4 and/or 5 on the C-SSRS.
- Participants must not meet criteria for current severe substance use disorder, anorexia nervosa, or active psychosis as captured by the MINI.
- Participants may not currently be in psychotherapy and have not received any other psychotherapy and/or stimulation (ECT, TMS) within the last 4 weeks.
- Any participants taking psychotropic medication must be on a stable dose for at least 4 weeks with no planned dose changes within the next 4 weeks.
- (for female participants) Participants must not be pregnant or breastfeeding.
- Participants may not have any medical or neurological illness for which symptom presentation or treatment could interfere with study participation
- Participants may not have undergone prior brain surgery
- Participants may not have any brain devices/implants, including cochlear implants and aneurysm clips
- Participants may not have had brain injury or concussion within the last three months
- Participants may not have a history of brain injury requiring current treatment

5.3. Enrollment/Selection Strategies

5.3.1. Prospective Recruitment -or- Retrospective Selection

To aid in recruitment, we will advertise the study directly to the public on websites such as ClinicalTrials.gov, frohlichlab.org and Carolinaneurostimulation.org. We will have contact information and a summary of the clinical trial

posted on the Frohlich Lab social media pages. We may also be launching a social media ad to identify potential patients. This ad will also use a pre-screening survey via REDCap to help identify participants. We will also be using the UNC Mass email listserv and an IRB-approved registry. All patient identifiers will be stored in REDCap until recruitment is over. When recruitment is over, all patients who do not consent or are not eligible for participation in the study will have their responses permanently deleted in REDCap.

5.3.2. Screen Failures

In the design of this study, initial phone screening procedures should identify the majority of participants who could potentially become screen failures if consented to participate in the clinical trial. However, the phone screening process does not necessarily account for all exclusion criteria. In the case that a participant meets initial criteria, there is still a chance that the first interview reveals that they do not meet study criteria. The study personnel completing the interviewing process will clearly explain why the participant does not meet criteria. However, in the case that a participant does not qualify based on suicide risk, procedures will be followed to ensure participant safety.

At the first session and after obtaining participant informed consent, the C-SSRS will be administered, which contains questions related to suicidal thoughts/actions. If someone indicates intent based on the C-SSRS, their participation in the study will be immediately stopped and Dr. Schiller (Co-I, responsible for participant safety) will be contacted for acute assessment. In the case that the person does not see anyone for their depression, Dr. Schiller will provide the participant with resources for seeking psychological care.

Assessment may include facilitating contact of the participant with their psychiatrist/primary care physician to establish a plan for safety, continued care, and follow-up. If the participant does not have an established provider, Dr. Schiller will assist the participant in establishing care. If at any point in the assessment, the participant is deemed to be an imminent risk of harm to self or others, study personnel will contact the Emergency Department for further care.

5.4.Strategies for Retention

Retention will be primarily achieved by the short duration of participation. Namely, the study includes a single intervention session, preceded by and followed by additional study visits. Participants will be paid $45 for participation in the initial study visit, $15 for the intervention/stimulation visit, and $30 for the two-week follow up visit. Participants will also be sent questionnaires to complete virtually 4 weeks after the intervention visit, and they will be paid $10 for completion of these questionnaires. Total payment for completion of all visits in the study totals $100. This virtual visit will reduce burden on participants to travel for an additional study visit. The participant will receive payment at the end of each session on a payment card that can be loaded. The research staff will also give each participant a reminder call or email for upcoming sessions. Each research staff member will be available for the participants to contact via email or phone.

5.5. Matching and Stratification

N/A

5.6. Randomization and Concealment

Mengsen Zhang, a Frohlich Lab member, will oversee the randomization of 40 6-digit codes, which will be used by the experimenters. These codes are directly linked to which treatment participants receive (sham/placebo or 10 Hz tACS at 1 mA) and will be entered into the MATLAB script. In addition, 10 codes will be generated in the event that a participant is randomized but discontinues the study. Data will be collected until we reach out target of 40 participants, but there will be no bias towards completion for the different arms (in the unlikely event that one of the arms has more dropout than the others). The assignment of each participant cannot be determined by looking at the codes (e.g., codes are not sequential, code assignment is not based on “odd” or “even” numbers). Thus, the study is both randomized and concealed by virtue of using random numbers generated by a computer. Mengsen Zhang has no other responsibility in the study other than providing these randomized codes. If Mengsen Zhang leaves the Frohlich Lab, another equivalent researcher who does not work with human participants will perform this task.

5.7. Blinding

This study is designed to be double-blind. This means that the participant and the researchers are unaware of each participant's assignment until the completion of all data collection. This is accomplished using the randomization codes described above. Furthermore, this study utilizes an active sham stimulation. This means that the active sham condition includes some stimulation, mimicking the skin sensations associated with tACS. In our previously concluded trial, participants in the delta-beta tACS and active sham groups responded similarly to the blinding questionnaire, indicating that our active sham stimulation successfully blinded the participants.

6. Treatment Design: Procedures

Description All participants will receive the behavioral activation (BA) psychotherapy intervention. This intervention occurs in a single 90-minute session. Participants are randomized to receive either an active stimulation or sham stimulation using transcranial alternating current stimulation (tACS).

Acquisition The DC-STIMULATOR MC is a CE-certified medical device is owned and operated by the Carolina Center for Neurostimulation / Frohlich lab.

Concomitant Therapies Participants will be ineligible to participate in this study if they are currently receiving another form of psychotherapy, TMS, and/or ECT. Individuals prescribed psychiatric medication must be on a stable dose (>4 weeks). Concomitant medications will be logged at the first session. Participants will be requested to include the dosing for these therapies (i.e., how often per day, how much in each pill, how many pills) as well as when they were first prescribed the medication.

7. Schedule of Activities and Procedures

7.1.Table of Events

Table 3. **Schedule of activities and procedures for a randomized clinical trial**

Procedure		Phone screening	Visit 0 baseline	Visit 1 Tx visit	Visit 2 2-week FU	Visit 3 4-week FU online
Recruit a Sample of Patients	Informed consent	X	X			
	Eligibility assessments	X	X			
	Enrollment and randomization		X			
Treatment	Administer regimens			X		
Clinician-Assessed Measures	Depressive symptoms		X		X	
	DSM-5 Diagnoses		X			
	Anhedonia symptoms		X		X	
Safety Monitoring	Review concomitant meds.		X	X	X	X
	Suicidality assessment		X	X	X	
	Assessment of AEs		X	X	X	X
Patient Reported Measures	anhedonia scores		X		X	X
	depression and anxiety scores		X		X	X
	Stress scores		X		X	X
	Rumination scores		X		X	X

[1, 2, 3, 4, 5] Footnotes that list and define the measures of interest are used here.

Screening
Participants that request to be in the experiment will provide verbal, documented consent to undergo a phone screening to assess that the participant meets exclusion/inclusion criteria. Participants who are initially deemed initially eligible due to meeting criteria for 5 or more MDD symptoms within Module A of the MINI will be invited to enroll within two weeks of phone screen date.

At the initial in-person visit, participants will provide written consent before completing additional assessments to confirm eligibility and for exploratory analyses. Self-report clinical assessments will be completed on REDCap while being monitored: Inventory of Depression and Anxiety Symptoms (IDAS; Watson et al., 2007); Behavioral Activation System and Behavioral Inhibition System (BIS/BAS; Carver and White 1994), Temporal Experience of Pleasure Scale (TEPS; Gard, Gard et al. 2006), the State-Trait Anxiety Inventory (STAI; Spielberger 2010), and Ruminative Responses Scale (RRS; Nolen-Hoeksema, Larson et al. 1999). Participants will also undergo clinician-administered assessments that will be entered onto REDCap: the Mini International Psychiatric Interview for the DSM-5 (MINI; Sheehan et al., 1998), Hamilton

Depression Rating Scale (HDRS; Williams, 1988), Snaith- Hamilton Pleasure Scale – Clinician Administrated (SHAPS-C; Ameli et al., 2014), Columbia-Suicide Severity Rating Scale (C-SSRS; Posner et al., 1999). Eligibility for the study is determined by a MINI diagnosis of MDD, exclusion based on a present severe substance use disorder, a present diagnosis of anorexia nervosa, and meeting criteria for current active psychosis. In addition, participants must not have active suicide risk as determined by the C-SSRS (see Inclusion/Exclusion criteria above). In the event that a participant has active plans to commit suicide, an adverse event is recorded, an acute psychiatric assessment is conducted by our medical monitor, Dr. Crystal Schiller, who is a clinical psychologist at UNC-CH, and participation is terminated.

Enrollment

After providing written informed consent, further clinical assessments will be conducted (e.g., clinician-administered depression assessment, MINI diagnostic assessment) to confirm eligibility for enrollment.

7.2. Study Visits

Following an eligible phone screen, participants will be scheduled to come in for the first in-person visit within two weeks of the screen. At the session, participants will provide written consent to participate in the study. They will undergo clinician-administered assessments: Hamilton Depression Rating Scale (HDRS), the Snaith-Hamilton Pleasure Scale (SHAPS-C), the Mini International Neuropsychiatric Interview for DSM-5 (MINI) and the Columbia-Suicide severity Rating Scale (C-SSRS). Exclusion criteria for severe SUD, AN, or current psychotic symptoms will be determined from the MINI. In addition, the participant must not have suicide intent as determined by the C-SSRS. At this visit, participants will also complete a reward-related decision-making task (S-EEfRT) during EEG collection. Participants will also complete self-report questionnaires on psychological symptoms.

At the intervention visit, which will occur within one week of the baseline visit, all participants will complete a single-session 90-minute BA treatment. During the second half of the intervention visit, stimulation will occur for a duration of 30 minutes. Participants will be randomized to receive either delta-beta tACS or an active sham stimulation. The C-SSRS will also be administered.

The third session occurs approximately two weeks after the intervention session. At the session, the HDRS, SHAPS-C and C-SSRS will be administered. Participants will complete a behavioral task while EEG data are collected and self-report questionnaires on psychological symptoms.

7.3. Final Visit

Four weeks after their participation in the intervention visit, participants will be emailed a link to complete self-report questionnaires to assess clinical outcomes through REDCap, a secure database web-platform.

7.4. Phone Contacts

N/A

7.5. Follow-Up Contact

N/A

7.6. Early Discontinuations

Data to be Collected If participants elect to withdraw from the study, the reason for discontinuation will be documented. No further follow-up data will be collected.

Criteria for Intervention Discontinuation

The study intervention (i.e., 90 minutes of BA with final 30 minutes of stimulation) will be discontinued for the following reasons:

• Any clinical adverse event (AE), laboratory abnormality, intercurrent illness or other medical condition, or situation occurs such that continued participation in the study would not be in the best interest of the participant.
• The participant meets any exclusion criteria (either newly developed or not previously recognized).

7.7. Enrollees May Drop Out

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

The reason for participant discontinuation or withdrawal from the study will be recorded with the participant files. Participants who sign the informed consent form and are not randomized will be replaced. Participants who sign the informed consent form, are randomized, and receive the full or part of the study intervention, and subsequently withdraw from the study, are withdrawn from the study, or discontinue the study will not be replaced.

8. Statistical Analysis Plans

8.1.Strategies that Apply to all the Aims

All testing described below assumes a significance threshold of p = 0.05. Analyses will be deemed to be statistically significant if the p-value is less than this threshold. An analysis that does not exceed this threshold will be considered inconclusive.

There may be additional covariates included in the analysis. Data will be assessed for normality and, if deemed necessary, corrective procedures will be applied (e.g., log normalization). Based on our previous dataset, we expect that the variables used here will be approximately Gaussian. However, if the distribution of a variable displays a skewed tail and a test for normality fails, then it is justified to use a corrective procedure. This correction will be applied upon consideration of the variables themselves, and not based on the result of the intended analysis.

Human studies are prone to drop-out, missing data, and interval-censored values. The reasons for drop outs, missing / censored data values, and protocol departures will be documented in the database. Best practices for dealing with incomplete data will depend on the documented causes of those occurrences.

The analysis plans will include outcome-dependent exploratory analyses to generate new hypotheses.

To help ensure replicability of the research, the analysis plans will be reviewed and finalized prior to collection of data (*a priori*). For each specific aim, the analysis plans specify detailed steps for obtaining estimates of the population parameters of interest (e.g., treatment effects) and for making inferences.

- Human studies are prone to drop-out, missing data, and interval-censored values. The reasons for drop-outs, missing / censored data values, and protocol departures will be documented in the database. Best practices for dealing with incomplete data will depend on the documented causes of those occurrences. In the analysis plans established *a priori*, the strategies for coping with incomplete data will be based on anticipated causes. Alternative methods for dealing with incomplete data will play important roles in the sensitivity analyses.
- All hypothesis tests yielding large p-values will be reported as being inconclusive. For all sample sizes, all hypothesis test procedures are (by design) incapable of establishing that the null hypothesis is true.
- If p-values are computed they should be reported to several decimal places without categorizing or dichotomizing the p-value; that is, the words “significant” and “non-significant” should be avoided. The p-value should be reported and interpreted as a continuous measure indicating the availability of information against

the (null) hypothesis being tested. The available amount of information against the null hypothesis is equal to the Shannon Information S-value, and the p-value = $(½)^{S\text{-value}}$. Smaller p-values (larger S-values) indicate greater amounts of available information. Larger p-values indicate a lack of information; e.g., if p = 1 then the S = 0. If p = 0.03125 then S = 5 which indicates a result that is as-surprising-as observing 5 'heads' in a row when flipping a coin 5 times to test whether it is a fair coin. Due to lack of information, large p-values cannot be used to draw any conclusions as to whether the tested null hypothesis is true or false. Lack of availability of evidence of an effect is not evidence of a lack of effect.

- The proposed statistical analysis strategy acknowledges that no p-value can reveal the plausibility, presence, truth, or importance of an association or effect --which is consistent with the statements of the American Statistical Association [4,5], the recommendations in Nature [6,7], and guidance, such as the CONSORT Statement [1], STROBE Statement [2], and ICMJE guidance [3].[†]]

8.2. Sample Description

Continuous data will be described using means, standard deviations, and confidence intervals, while categorical data will be described using counts/percentages.

8.3. Aim-Specific Plans

Plans for Aim 1 (PRIMARY).

Treatment response will be calculated as the depression (HDRS) scores from pre- to post-treatment. A two-way analysis of variance (ANOVA) will be performed using within-participant factor of time (before or after treatment), between-participant factor stimulation type (delta-beta tACS, active-sham), and the interaction between time and stimulation type. We hypothesize to find an interaction between time and stimulation type. Post hoc differences will be investigated. We hypothesize that the predicted interaction will be driven by a decrease in depressive symptoms for delta-beta tACS compared to the active-sham. Sensitivity analyses will be conducted to evaluate the specificity of these effects: a similar analysis with anxiety symptoms as the dependent variable and we do not expect that delta-beta tACS will have any effect on anxiety symptoms.

Further, we will conduct exploratory generalized linear mixed models will be conducted to examine potential confounds on treatment effect (e.g., age, sex, baseline depressive symptoms).

Plans for Aim 2 (SECONDARY).

Delta-beta phase amplitude coupling will be calculated between the phase of delta oscillations (2-3 Hz) in prefrontal electrodes (FCz and surrounding electrodes) and the amplitude of beta oscillations (15- 25 Hz) in left motor electrodes (C3 and surrounding electrodes). The instantaneous phase and amplitude of these oscillations will be calculated by averaging the signal in these two regions of interest, band-filtering the signal to the specified range, and then performing the Hilbert transform on the signal. Phase-amplitude coupling (PAC) is then calculated by creating a hybrid signal using the amplitude of beta oscillations in left motor electrodes and the phase of delta oscillations in prefrontal electrodes:

[†] [1] www.consort-statement.org , [2] www.strobe-statement.org, [3] www.icmje.org

[4] Wasserstein RL, et al. (2016), The ASA's Statement on p-Values, ***The American Statistician***, 70:2, 129-133.

[5] Wasserstein RL, et al. (2019), Moving to a World Beyond p < 0.05, ***The American Statistician***, 73:sup1, 1-19.

[6] Amrhein, et al. (2019), Scientists rise up against statistical significance, ***Nature*** 567, 305-307.

[7] Editorial (2019) It's time to talk about ditching statistical significance: … ***Nature*** 567, 283-283.

$PAC = \left|\frac{\sum_{t=1}^{N} M * e^{i\theta}}{N}\right|$ M is magnitude of beta oscillations, θ is angle of delta oscillations, N is number of time points

The PAC value is normalized by creating a null distribution by randomly shifting the beta timeseries by at least 10% of the number of time points. Then, PAC is calculated between the delta-phase timeseries and each of these randomly shifted beta-amplitude timeseries. Finally, PACZ is calculated as the z-transformed true PAC value relative to the null distribution.

A two-way analysis of variance (ANOVA) will be performed using within-participant factor of time (before or after treatment) and between-participant factor stimulation type (delta-beta tACS, active-sham). We hypothesize to find an interaction between time and stimulation type. Post hoc differences will be investigated. We hypothesize that the predicted interaction will be driven by an increase in delta-beta coupling for delta-beta tACS compared to the active-sham. Sensitivity analyses will be conducted to evaluate the specificity of these effects: a similar analysis with theta-gamma coupling as the dependent variable and we do not expect that delta-beta tACS will have any effect on theta-gamma coupling.

Further, we will conduct exploratory generalized linear mixed models will be conducted to examine potential confounds on treatment effect (e.g., age, sex, baseline depressive symptoms).

Plans for Aim 3 (SECONDARY).

Goal-directed behavior will be calculated as the average decision to perform the HARD task across blocks. A two-way analysis of variance (ANOVA) will be performed using within-participant factor of time (before or after treatment) and between-participant factor stimulation type (delta-beta tACS, active-sham). We hypothesize to find an interaction between time and stimulation type. Post hoc differences will be investigated. We hypothesize that the predicted interaction will be driven by an increase in goal-directed behavior for delta-beta tACS compared to the active-sham. Sensitivity analyses will be conducted to evaluate the specificity of these effects: a similar analysis with reward-evaluation as the dependent variable and we do not expect that delta-beta tACS will have any effect on reward-evaluation.

Further, we will conduct exploratory generalized linear mixed models will be conducted to examine potential confounds on treatment effect (e.g., age, sex, baseline depressive symptoms).

Plans for Aim 4 (EXPLORATORY).

Exploratory analyses are planned only if effects are seen on depressive symptoms (Aim 1). If so, we plan to explore the potential effects specific to anhedonia symptoms. Treatment response will be calculated as the change in anhedonia (SHAPS-C) scores from pre- to post-treatment. A two-way analysis of variance (ANOVA) will be performed using within-participant factor of time (before or after treatment) and between-participant factor stimulation type (delta-beta tACS, active-sham). We hypothesize to find an interaction between time and stimulation type. Post hoc differences will be investigated. We hypothesize that the predicted interaction will be driven by a decrease in anhedonia symptoms for delta-beta tACS compared to the active-sham.

Further, we will conduct exploratory generalized linear mixed models will be conducted to examine potential confounds on treatment effect (e.g., age, sex, baseline non-anhedonic depressive symptoms).

Exploratory analyses with anhedonia symptoms will not be conducted if effects for overall depressive symptoms (Aim 1) are not found.

Planned Interim Analyses

No interim analyses will be performed.

9. Sample Size Rationale

The experiment proposed here will utilize a parallel arm design, and primary analyses will use a repeated-measures ANOVA with one within-participant factor (before and after treatment) and one between-participants factor (delta-beta, placebo). With an average effect size of 0.286 partial-eta square estimated from existing literature on single session BA, we estimate that we need at least 15 participants per group to achieve 80% statistical power. Using a conservative estimate of 0.5 correlation between estimates, we still reach ~99% power with 40 participants (Figure 3). Data will be collected until we reach 40 participants. Given the similarity in stimulation methodology between the current experiment and our previous experiment (Riddle et al., 2021), we anticipate adequate levels of power for hypothesis testing with 40 participants. Moreover, other studies of combined psychotherapy and stimulation have reported similar sample sizes (Neacsiu et al., 2022).

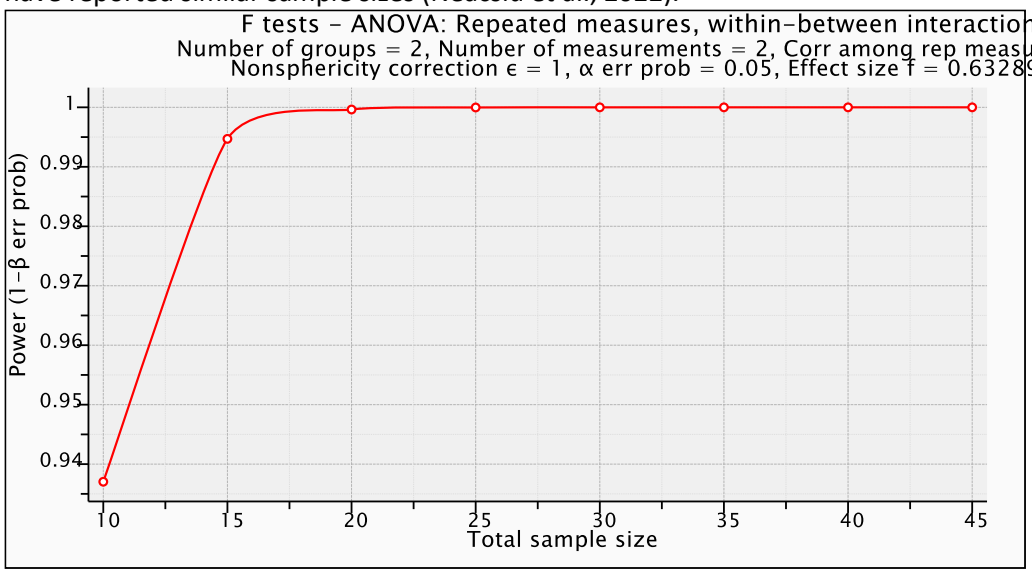


Figure 3. Power analysis for impact of BA + tACS on depressive symptoms with ANOVA.

10. Data Capture and Database Management

10.1. Software for Data Capture

The study data will be entered into a REDCap database developed by the study personnel. REDCap is a 21 CFR Part 11-compliant data capture system provided by the NC TraCS Institute at UNC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Study data will be entered directly from the source documents.

10.2. Responsibilities for Data Capture and Database Management

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by the TraACS. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.3. Study Records 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, records will be kept for three years after the completion of the study or grant end date, whichever is later.

11. Collection and Management of Tissue Specimens

11.1. Use in Current and Future Studies

N/A

11.2. Sample Preparation

N/A

11.3. Record Keeping and Monitoring

N/A

11.4. Storage and Security

N/A

12. Safety Monitoring and Management

12.1. Risk / Benefit Assessment

Potential Risks: Risk of Confidentiality Breach: In the unlikely event of a breach of confidentiality, people might discover that an individual was involved in this research study. This is especially sensitive because the clinical population recruited for this study may be subjected to negative consequences caused by the stigma of mental disorders. Furthermore, some might not agree with the principle of participating in research or of changing natural

brain activity. To avoid breaches in confidentiality, study documents that contain personal information and including the informed consent document are kept in locked filing cabinets in locked rooms separate from any source documents containing participant dummy identifiers. The document that links study ID numbers to personal identifying information is encrypted and protected using a password-protected document on a secure server provided by UNC School of Medicine. All data is stored in locked cabinets inside locked offices; electronic data will be stored only on password-protected computers, and data encryption methods will be used during communication between investigators. Only study personnel will have access to the data. All study staff participate in annual human participant training that includes education about responsibilities to the minimize risk of confidentiality breach. Risk of Embarrassment: Self-report assessments contain questions regarding sensitive personal information. This risk is necessary in order to assess mood symptoms and associated psychopathology. Participants will be assured upon intake that only study personnel will see any clinical ratings and that self-identifying information will not be collected alongside HIPAA protected information.

Risk of Injury and Discomfort: The side effects of tACS are mild and transient; in fact, low intensity transcranial current stimulation, such as tACS, has been used for over a decade without any report of serious side effects (Antal, Alekseichuk et al. 2017). Furthermore, 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 cause super-threshold activation of neurons (Frohlich and McCormick 2010). However, tACS does have some mild side effects, such as transient mild tingling, burning, or itching under the electrode sites. In our previous trial, participants from all three groups of stimulation reported either absent or mild side effects, and there was no difference between the groups with the exception of “flickering lights” (or phosphenes, $p = 0.014$) (Alexander, Alagapan et al. 2019). To monitor these mild side effects, we will be administering a stimulation questionnaire after each stimulation session to determine whether these effects were experienced and at what intensity. Research personnel present during these sessions will also check in with the participant periodically during the stimulation to see whether they are comfortable. If participant is experiencing severe discomfort (as determined by the questionnaire or by self-report), the stimulation will be stopped immediately.

Potential Benefits: This study has not been designed to benefit the individual participants. However, the knowledge gained from this study will contribute to understanding about the psychological and biological basis of depression. Furthermore, the results from this study might be used to inform future interventions using a combination of brief psychotherapy and non-invasive brain stimulation.

12.2. Assessment of Safety

1. The Columbia Suicide Severity Rating Scale (C-SSRS) (Posner, Brown et al. 2011) will be administered by trained research personnel at each session to thoroughly assess suicide risk. If a participant reports experiencing either suicidal ideation or suicidal behavior, research personnel will collect more information from the participant to deliver to either Dr. Schiller. Clinical personnel will decide if an acute assessment is required. Acute assessment may include facilitating contact of the participant with their psychiatrist or primary care physician to establish a plan for safety, continued care, and follow-up. If the participant does not have an established provider, Dr. Schiller will assist in establishing a care plan. If at any point during the assessment, the participant is deemed an imminent risk of harm to self or others, study personnel will enlist the aid of campus security to ensure that the participant is safely escorted to the Emergency Department for further care. Dr. Schiller will decide if participation should be stopped after the acute assessment. If an acute assessment is required, then participation will be halted.

2. A stimulation side effects questionnaire will be administered at the end of each stimulation session. This tool will be used as a safety measure and to collect data on the participant’s experience. A similar questionnaire was used in a previous study (IRB# 13-2995) to determine ability to successfully blind the participants using sham transcranial current stimulation.

3. We screen and exclude individuals with any medical or neurological illness for which symptom presentation or treatment could interfere with study participation. We further emphasize that there has never been a single report of a

seizure that resulted from transcranial alternating current stimulation (Matsumoto & Ugawa, 2016), and existing guidelines suggest that both tACS and tDCS are safe (Antal et al., 2017).

12.3. Unanticipated Problems, Adverse Events, Serious Adverse Events

Unanticipated Problems: The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants 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 Institutional Review Board (IRB)- approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

• Related or possibly related to participation in the research ("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 participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Adverse Event (AE) Definitions: Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether considered intervention-related (21 CFR 312.32 (a)).

Serious Adverse Events (SAE) Definition: An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Grading the Severity of Adverse Events and Events of 'Special Interest':

All adverse events (AEs) will be assessed by the principal investigator and/or co-investigator(s) using the following guidelines:

• Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.

• Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

• Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Relatedness Definition:

All adverse events (AEs) must have their relationship to study intervention assessed by the principal investigator and co-investigator(s) who examines and evaluates the participant based on temporal relationship and their clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

• Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be

explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

• Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

• Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

• Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

• Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Expectedness Definition: The principal investigator (Dr. Frohlich), with input from the co-investigators (Dr. Schiller, Dr. Riddle) when necessary, will determine whether an adverse event (AE) is expected or unexpected in this population. The principal investigator (Dr. Flavio Frohlich) is an expert in non-invasive brain stimulation and will provide his expert opinion in regard to this as well. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

AE and SAE Assessment, Follow-up Procedures:

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits, or the study participant may report AE or SAEs outside of a scheduled study visit.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution. Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Research personnel will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, research personnel will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's

assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Research personnel will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Reporting and Documentation Procedures: We will be adopting the following reporting procedures:

What event is reported	When is event reported	By whom is event reported	To whom is event reported
Fatal or life-threatening unexpected, suspected serious adverse reactions	Within 24 hours of initial receipt of information	Investigator	Local/internal IRB
Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions	Within 48 hours of initial receipt of information	Research Personnel	Local/internal IRB
Unanticipated adverse devise effects	Within 7 working days of investigator first learning of effect	Investigator	Local/internal IRB
Unanticipated problem that is not an SAE	Within 7 days of the investigator becoming aware of the problem	Investigator	Local/internal IRB

Participant Notification of New Information: Any new information gained during the study that may affect a participant's willingness to continue in the study will be reported to all currently enrolled participants.

12.4. Safety Monitoring

1. The Columbia Suicide Severity Rating Scale (C-SSRS) (Posner, Brown et al. 2011) will be administered by trained research personnel at the first session to thoroughly assess suicide risk. If a participant reports experiencing either suicidal ideation or suicidal behavior, research personnel will collect more information from the participant to deliver to either Dr. Schiller. Clinical personnel will decide if an acute assessment is required. Acute assessment may include facilitating contact of the participant with their psychiatrist or primary care physician to establish a plan for safety, continued care, and follow-up. If the participant does not have an established provider, Dr. Schiller will assist in establishing a care plan. If at any point during the assessment, the participant is deemed an imminent risk of harm to self or others, study personnel will enlist the aid of campus security to ensure that the participant is safely escorted to the Emergency Department for further care. Dr. Schiller will decide if participation should be stopped after the acute assessment. If an acute assessment is required, then participation will be halted.

2. A stimulation side effects questionnaire will be administered at the end of each stimulation session. This tool will be used as a safety measure and to collect data on the participant's experience. A similar questionnaire was used in a previous study (IRB# 13-2995) to determine ability to successfully blind the participants using sham transcranial current stimulation.

Study Suspension / Early Termination of the Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform research staff, study participants, and the IRB and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

13. Regulatory, Ethical, and Study Oversight Specifications

13.1. Informed Consent Process

13.1.1. Consent/Assent and Documents Provided to Participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

13.1.2. Consent Procedures and Documentation

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 and their families. 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. Verbal consent will be documented prior to conducting the phone screenAll consent forms will be IRB-approved and updated with any new information as modifications are made throughout the study.

During a phone call, the researcher and potential participants will review the clinical trial in its entirety. At several intervals during the consent review, the researcher will ask questions that will assess the comprehension of the information in the consent. If the participant is unsure or does not know, the researcher will return to that section and more carefully explain the information. If needed, the participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice.

At the beginning of the first visit to the lab, participants will sign a physical copy of the consent document witnessed by research personnel. A copy of the signed informed consent document will then be given to the participant for their records. The rights and welfare of the participant will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.2. Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform research staff, study participants, and the IRB and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

13.3. Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in the TraCS Clinical Research Data Management Service (REDCap). This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by TraCS research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Carolina Center for Neurostimulation/Frohlich Lab.

13.3.1. Certificate of Confidentiality

A certificate of confidentiality will be obtained prior to the start of data collection.

13.4. Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored within the Carolina Center for Neurostimulation/Frohlich Lab. After the study is completed, the data will be fully de-identified and archived within a locked file cabinet or an encrypted server maintained by the Carolina Center for Neurostimulation. Biological samples will be stored at the Carolina Center for Neurostimulation/Frohlich lab and at UNC's Neurosciences Hospital. Samples will be not be stored for future research.

13.5. Key Roles and Study Governance

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13.6. Safety Oversight

Safety oversight will be under the direction of the principal investigator and co-investigators composed of three clinical researchers. The PI and/or Co-I will review AEs in real time and make decisions as of participant's continuation of the clinical trial. The PI will review AEs as appropriate, every three months at a minimum, with the research team. The PI may request additional review by Co-I on a case-by-case basis.

13.7. Clinical Monitoring Plan (CMP)

The purpose of the monitoring plan is to present the approach of the Carolina Center for Neurostimulation to monitoring clinical trials. The plan facilitates compliance with good clinical practice.

(a) The rights and well-being of human participants 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 in the hands of the trained research personnel. 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. Deviations will be sent to IRB every 4-6 weeks (if necessary).

Data will be verified for completeness following every study session and all data will be entered into REDCap, a secure online database. After a participant has completed their participation (full completion through the 2-week follow-up visit or because they withdrew prior to completion), data will be rereviewed for completeness and accuracy. After all data has been collected, data will be re-reviewed by another lab member who was not involved with the data collection process.

AE and SAE are clearly defined in the Master Protocol. Documents of AE and SAE can be found in the study binder on file within 77 Vilcom Center, Suite 170, Room 110. It is responsibility of trained research personnel to report all events to the PI. Reporting of AEs and SAEs is described within Section 12.3.

The PI and Co-I will have read-only access to the REDCap database. This allows the PI and Co-I to view reports that provide information on any missing data on an individual participant basis, but does not allow them to add, change or input any data.

13.8. Quality Assurance and Quality Control

The Carolina Center for Neurostimulation will conduct internal quality management of study conduct, data and biological specimen collection, documentation and completion. Following written Standard Operating Procedures (SOPs), research personnel will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

13.9. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

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.

13.10. Publication and Data Sharing Policy

This trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

13.11. Conflict of Interest Policy

The independence of this study from any actual or perceived influence is critical. Any conflict of interest for any persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed by the UNC Conflict of Interest Office. If necessary, for persons who have a perceived conflict of interest, management will be provided again by the UNC Conflict of Interest office.

14. Additional Considerations

N/A

15. References

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16. Appendices

N/A