Enhancing Neural Synchrony and Affective Cognitive Control in Bipolar Disorder using Personalized Transcranial Alternating Current Stimulation (tACS)

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Enhancing Neural Synchrony and Affective Cognitive Control in Bipolar Disorder using Personalized Transcranial Alternating Current Stimulation (tACS)

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Investigational Agent: Soterix, Medical High-Definition Transcranial Alternating Current Stimulation device (HD-tACS)

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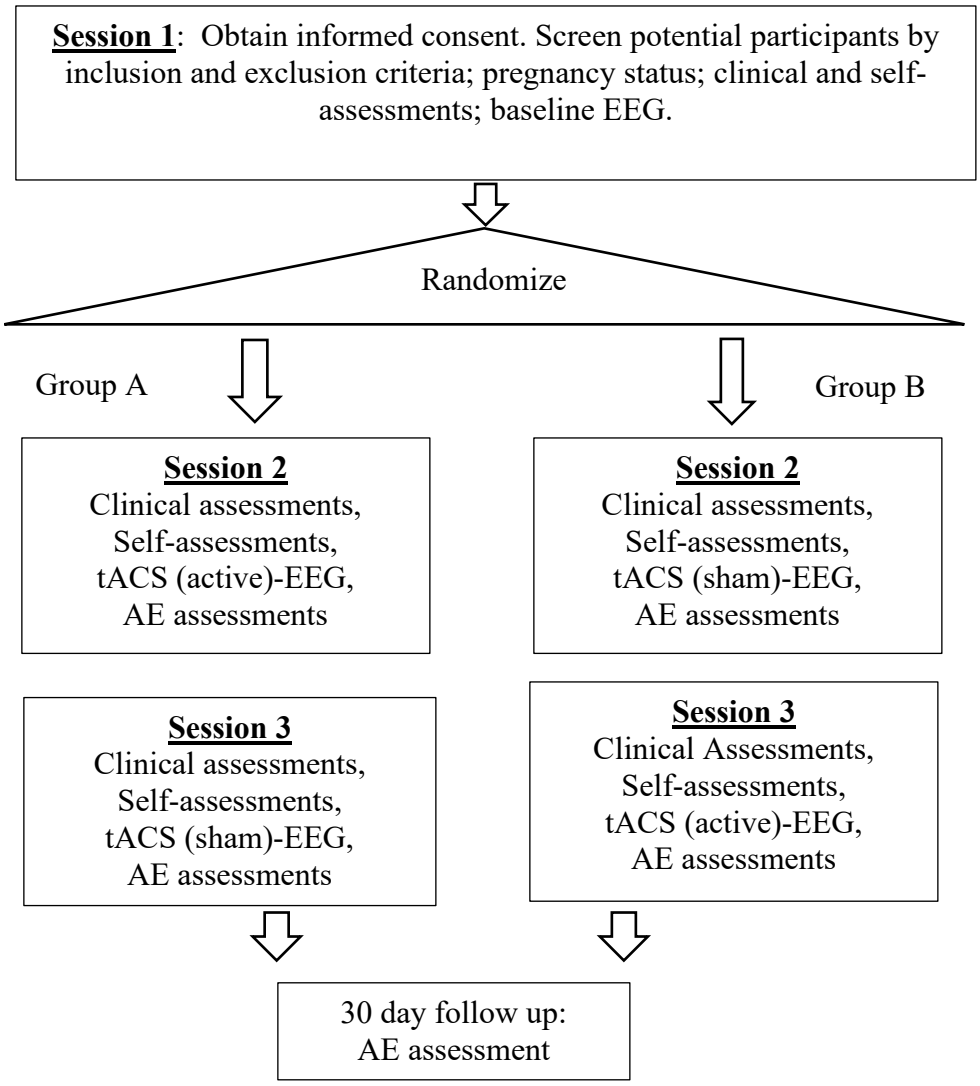
STUDY SYNOPSIS

Title	Enhancing Neural Synchrony and Affective Cognitive Control in Bipolar Disorder using Personalized Transcranial Alternating Current Stimulation (tACS)
Study Design	The randomized, double-blind, sham-controlled, cross-over study will involve three sessions. The first session will involve a clinical interview, questionnaires, and EEG recording during a computerized task. The second and third sessions will involve tACS brain stimulation (or placebo stimulation) during a computerized task and EEG recording.
Study Duration	Enrollment duration: 12 months Subject follow-up duration: 1 month Estimated duration until study completion: 12 months
Study Center(s)	Single center
Aims	Aim #1: Evaluate the feasibility and acceptance of tACS among bipolar patients. Aim #2: Estimate the preliminary effects of personalizedtACS on theta-gamma phase-amplitude coupling (PAC) and cognitive control behavior in bipolar disorder (BD).
Number of Subjects	30
Disease/condition	Bipolar Disorder
Inclusion/Exclusion Criteria	See Section 3.0 for a complete list of inclusion and exclusion criteria
Description of Study Intervention:	HD-tACS will be used to deliver current (active vs. sham) to the electrodes to generate tACS most closely approximate endogenous neural activity. Participants will be fitted using a montage consisting of 5-9 electrodes placed over the right frontal and temporal scalp.
Duration of Study	approximately 6 weeks
Statistical Methodology	Aim 1: We will compare the percentage of participants requesting to discontinue the session and the number of mild and severe adverse events reported during and following the tACS vs. sham procedure using Bayes factors (BF). Aim 2: EEG data preprocessing and spectral analyses will be conducted using custom MATLAB scripts and EEGLAB following the general methods described in PI Tso's published work.

STUDY SCHEMA



1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Bipolar disorder (BD) is an impairing neuropsychiatric condition with high rates of relapse, morbidity, and mortality. Treatment of BD is challenging due to its complex clinical presentations and variable response to traditional pharmacologic treatments across individuals. Effective, personalized interventions are severely hindered by our lack of mechanistic insight of the disorder.

1.2 Study Agent(s) Background and Associated Known Toxicities

Recent groundbreaking work showed that transcranial alternating current stimulation (tACS), a non-invasive neuromodulation, can be programmed such that its wave patterns mimic natural theta-gamma coupling, a critical neural mechanism of cognitive control [4,16]. Critically, applying frontal tACS targeting individualized peak theta/gamma coupling frequencies is able to enhance theta-gamma coupling and improve cognitive control performance among healthy non-psychiatric participants. These findings provide support for tACS's ability to modulate the neural underpinning of cognitive control in humans. This study will pursue critical next step towards realizing this potential therapy by demonstrating both feasibility (safety and tolerability) and efficacy of personalized tACS in engaging the neural target of affective cognitive control-related neural synchrony in BD patients.

1.3 Rationale

A growing body of research suggests that deficient cognitive control, the ability to modulate cognitive and emotional processes in order to optimize behavior and enhance adaptation with respect to the current context, may be a key mechanism contributing to these characteristics of BD. Specifically, behavioral studies strongly indicate that cognitive control, expressed as response inhibition, is impaired in BD[1] and associated with impulsivity and illness outcome.[2,3] Therefore, understanding and leveraging the neural underpinnings of cognitive control is a promising avenue to developing neurobiologically-informed and precise treatments that target the underlying network dysfunction.

We have shown in a series of EEG studies that frontal theta-band (4-8 Hz) neural oscillatory activity and phase-amplitude coupling with gamma (30-60 Hz) activity are reduced in bipolar disorder during socio-emotional processes requiring cognitive control. This provides support that theta-gamma coupling is a promising neural target to engage for BD. Recent groundbreaking work showed that transcranial alternating current stimulation (tACS), a non-invasive neuromodulation, can be programmed such that its wave patterns mimic natural theta-gamma coupling, a critical neural mechanism of cognitive control. Critically, applying frontal tACS targeting individualized peak theta/gamma coupling frequencies is able to enhance theta-gamma coupling and improve cognitive control performance among healthy non-psychiatric participants. These findings provide support for tACS's ability to modulate the neural underpinning of cognitive control in humans. This study will pursue critical next step towards realizing this potential therapy by demonstrating both feasibility (safety and tolerability) and efficacy of personalized tACS in engaging the neural target of affective cognitive control-related neural synchrony in BD patients.

1.4 Objective

This project will provide a critical proof of concept that personalized tACS is feasible and effective in engaging the neural target of theta-gamma coupling in BD patients, and importantly, helping them to

regain cognitive control. The ultimate goal of this research is to make this innovative and customizable treatment modality widely accessible for individuals living with BD.

2.0 STUDY DESIGN, AIMS AND OUTCOME MEASURES

The randomized, double-blind, sham-controlled, cross-over study will involve three sessions. The first session will involve a clinical interview, questionnaires, and EEG recording during a computerized task. The second and third sessions will involve tACS brain stimulation (or placebo stimulation) during a computerized task and EEG recording. Participant's psychiatric phenotypes and functioning will be dimensionally characterized. Affective cognitive control in bipolar disorder will be assessed using the Emotion Go-NoGo Task.

Aim #1: Evaluate the feasibility and acceptance of tACS among bipolar patients. Neuromodulation studies typically use dropout rate and reported adverse events as measures of acceptability and tolerability, respectively[10]. We will compare the percentage of participants requesting to discontinue the session and the severity of side effects reported following the tACS vs. sham procedure using Bayes factors (BF).

Intervention: One-session tACS
Primary outcome measure 1: Severity of side effects reported at end of stimulation session. This is calculated by summing the severity score of items (0-4) that are rated by the participant as related to stimulation (ratings of 3=probable or 4=definite) on the Stimulation Side Effects Questionnaire.
Primary outcome measure 2: Withdrawal during or after the stimulation session.

Aim #2: Estimate the preliminary effects of personalized tACS on theta-gamma phase-amplitude coupling (PAC) and cognitive control behavior in BD.

Intervention: One-session tACS
Primary outcome measure 3: Accuracy signal detection theory metric sensitivity (d') derived from the behavioral responses to Go and NoGo trials on the cognitive control task.
Primary outcome measure 4: Accuracy signal detection theory metric response bias (β) derived from the behavioral responses to Go and NoGo trials on the cognitive control task.
Primary outcome measure 5: Reaction time (millisecond) of Go trials on the cognitive control task.
Primary outcome measure 6: Theta-gamma PAC (Kullback-Leibler Modulation Index) during the rest EEG blocks interleaved between stimulation blocks.

3.0 SUBJECT ELIGIBILITY

Subjects must meet all the selection criteria to be enrolled to the study. Study treatment may not begin until a subject has been consented and meets the full eligibility criteria.

3.1 **Inclusion Criteria**

Participants will be: (1) Age 18-55 inclusive; (2) Ability and willingness to give informed consent; (3) Confirmed diagnosis of BD based on DSM-IV criteria being met from previous enrollment in the Prechter Bipolar Longitudinal Study (HUM00000606, PI: McInnis); (4) We will select BD patients scoring above published norms (upper 50th percentile) on the NEO-PI impulsivity facet [6] to ensure that

the recruited patients exhibit the network dysfunction targeted by the tACS paradigm and therefore have the potential to benefit from this neuromodulation technique. (5) On a stable dose of medication for 2 weeks prior to Sessions 2 & 3.

3.2 **Exclusion Criteria**

Participants will not have: (1) Significant neurological abnormalities, such as seizure disorder, mass lesions, etc.; (2) Known Mendelian disorder; (3) Active problematic substance use in the past 30 days (as determined by the Substance Use Disorder module of SCID); (4) Evidence of suicidal intentions or behaviors in the past month, as judged by affirmative responses to question #4 or #5 on the Columbia Suicide Severity Rating Scale (CSSRS) or report of suicidal behaviors in the last 6 months (refer to Appendix A for suicide protocol); (5) Pregnant or trying to become pregnant, or currently lactating; (6) unremovable hair extensions, braids or weaves; (7) implants or neurostimulators which could interact with applied electrical currents; (8) history of serious traumatic brain injury (loss of consciousness > 20 min)

4.0 SUBJECT SCREENING, ENROLLMENT, AND RECRUITMENT

We will recruit 30 individuals with a DSM-IV diagnosis of Bipolar Disorder (I, II, or NOS) from the Prechter Longitudinal Bipolar Disorder Study which consists of a cohort of 800+ well-characterized BD patients.[5]

4.1 **Screen Failures**

Those found to be ineligible to participate after the Session 1: Screening & Assessment visit will still be compensated a total of $20 for their time. Those who leave the study early will be paid for the sessions they completed.

4.2 **Blinding**

Participants, study coordinator and clinical assessor will be blind as to which session the participants receive active or sham treatment. The PI and the data analyst will be aware of the intervention assignment.

4.3 **Subject Recruitment and Retention**

We will recruit 30 individuals with a DSM-IV diagnosis of Bipolar Disorder (I, II, or NOS) from the Prechter Longitudinal Bipolar Disorder Study which consists of a cohort of 800+ well-characterized BD patients.[5] Participants are expected to match the sex and racial composition of the Longitudinal study (50% female, 50% male; 81% white, 12% African-American, 6% Asian, 1% Other). Participants who are enrolled in the Prechter Study, and who have been identified by the Prechter Study staff as possible participants, will be emailed a description of this study, including contact information about how to learn more.

Pre-screening will occur when the study coordinator contacts the potential participant, via phone or email to discuss a series of eligibility questions. Patients who appear eligible in the pre-screen will be invited for an initial assessment session. Reminder calls, emails and/or texts will be provided to subjects before each scheduled session.

5.0 STUDY ASSESSMENTS AND PROCEDURES

5.1 **Assessments**

Clinician Administered Assessments (~ 60 mins):

1) Demographic/medical history form
2) Structured Clinical Interview for DSM-IV (SCID-IV), substance use disorder only (Module E). *Note: Subjects endorsing unhealthy substance use in the last 30 days but do not meet full criteria for abuse or dependence will be given a urine drug screen.*
3) The Mental Illness Research, Education and Clinical Centers Global Assessment Functioning (MIRECC GAF)
4) Social and Occupational subscales only Young Mania Rating Scale (YMRS) – scale to grade the severity of mania symptoms
5) Hamilton Depression Rating Scale (HAM-D) – scale to grade severity of depression
6) Columbia-Suicide Severity Rating Scale (C-SSRS)

Self-Rated Assessments (~ 30 mins):

1) Beck Depression Inventory (BDI)
2) Altman Self-Rating Mania Scale (ASRM)
3) Barratt Impulsiveness Scale (BIS)
4) Behavioral Inhibition System/Behavioral Activation System (BIS/BAS)
5) Stimulation Side Effects Questionnaire
6) Penn State Worry Questionnaire (PSWQ)

5.2 **Procedures**

The following procedures will be conducted in-person following the University of Michigan's Covid safety protocols.

Pre-Visit Preparations. Participants who meet criteria after initial phone screening, will be scheduled for three in-person sessions at the Rachel Upjohn Building. Participants will be emailed a blank copy of the consent form to review prior to their visit.

Session 1: Screening & Assessment (~ 2-3 hours)

1) *Informed Consent.* Formal consent will be obtained at the beginning of the visit. The participant will arrive at the Rachel Upjohn Building at the University of Michigan East Ann Arbor Health Campus. A study coordinator or a trained research assistant will greet the participant and take them to a private interview room where the study will be explained, the consent form reviewed, and any questions answered. Participants will have the option to electronically consent (using SignNow, according to IRBMED guidelines) prior to the in person visit through a Zoom meeting with one of the study team members.
   Pregnancy Screening. All woman of childbearing age will be asked during their screening whether they are pregnant or are trying to become pregnant and will not be enrolled in the study if they are. They will be given an option for a urine pregnancy test at the start of each session. Woman with a positive pregnancy test will not be permitted in the study. They may decline this option and sign a pregnancy attestation form at each session indicating that they do not believe they could be pregnant.

Sexually active women of childbearing potential will be required to use a reliable birth control method for the duration of this study.

2) *Clinician Administered Assessments*. This interview process will be conducted to determine a participant's inclusion/exclusion eligibility. If the participant is ineligible to participate in the study, the rationale for their exclusion will be explained to them.

3) *Urine Drug Screening (UDS).* Participants who screened positive for current substance use disorder will be administered a UDS. If their UDS indicates the presence of a substance, they will not undergo that day's visit. At the PI's discretion, the participant may be given the option to abstain from all substance use and be rescheduled to provide another urine sample. If they have a clean UDS at that time, they will be able to continue with the visit at that time. Those that are not given the option or who refuse to do the UDS will be a screen fail. Participants who have no active current substance use will not be required to provide a urine sample.

4) *Self-Rated Assessments*. Participants deemed eligible will complete self-rated assessments and computerized tasks through Qualtrics, using an anonymous survey link. No identifiable information will be collected within the survey.

5) *Baseline EEG*. EEG will be recorded using a 64-channel electrode cap using EEG procedures that are standard in cognitive ERP and time-frequency analysis research. The cap is an elastic cap that fits snugly over the scalp of the participant, holding the electrodes in place. A standard conductive electrode gel will be inserted into each electrode using a blunt-needle syringe. The scalp will be gently rubbed with a swab to improve electrode impedance (i.e., to lower the electrical resistance). Typical application time for an electrode cap lasts around 30 minutes. The electrode for monitoring eye movements will be affixed with adhesive collars. The skin will also be cleaned with an alcohol swab for this electrode. The cap and electrodes will be disinfected after each use with a disinfectant recommended by BrainVision Company (e.g., Cavicide). Other items will be disposed of after each use. The experimenter will wipe the residual electrode gel from the participant's hair and skin after the EEG session.

   Emotion Go-NoGo Task. Participants will undergo an EEG and perform a cognitive control task (Emotion Go-NoGo task; described below).

   Flanker Task. After completing the Emotion Go-NoGo task, participants will perform a separate cognitive control task (i.e., Flanker task; described below). Accuracy and reaction time will be used to index cognitive control behavior as outcome measures. EEG recorded during the Flanker task will be used to assess neurological indicators of attention control. Participants will then be 50-50 randomized to receive either the Sham treatment first or tACS treatment first at Session 2.

7) *Randomization.* Subjects will be randomized on a 50-50 basis to receive active vs. sham stimulation. If participants are randomized to the active group at Session 2, they will go to the sham group at Session 3, and vice versa. The participant will not be told which group they were randomized to. The randomization schedule will ensure an equal distribution across the group. Randomization lists

will be generated by random condition generator and will be programmed into the computer that controls the tACS device by the postdoc fellow or PI.

Sessions 2 and 3: Sham vs. Active tACS Session (~ 2-3 hours)

These sessions will occur at the University of Michigan Rachel Upjohn Building. Participants will undergo two sessions, separated by ~ 1 week. Procedures will be identical for each session.

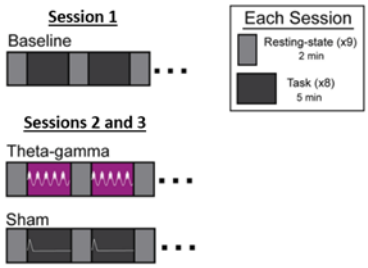
1) *Pre-Visit Preparations.* Research staff will contact the participant to remind them about the study visit and to ask if they have had any medication changes since their last visit. If yes, the participant will be re-scheduled for an appointment time in which the criteria for a stable dose of at least two weeks has been achieved. Additionally, participants will also be asked if they have had any recreational drug use since their last study visit. If yes, the participant will have to be re-scheduled 30 days out.

2) *Arrival on scheduled session day.* Participants will arrive at the Rachel Upjohn Building where they will be greeted by a member of research staff and escorted to the treatment room. Pregnancy urine test will be given if participant opted out of signing the Pregnancy Attestation Form.

3) *Clinician Administered Assessments.* In-person clinical assessments will be completed by a trained member of staff. All study clinicians are blinded to the treatment arm.

4) *Self-Rated Assessments.* Participants will fill out BDI, ASRM, and PSWQ questionnaires. Any additional questionnaires not completed at the previous visit may be completed at this time or given to the participants to complete at home.

5) *EEG and brain stimulation*. EEG procedures will be repeated from Session 1. CF (cross frequency)-tACS targeting theta-gamma PAC will be administered in accordance to Consultant Frohlich's published protocol[4], which has successfully enhanced theta-gamma PAC and cognitive control in non-psychiatric individuals. Participants will be fitted using a montage consisting of 9 electrodes placed over the left frontal scalp.



Soterix Medical High-Definition Transcranial Alternating Current Stimulation device (HD-tACS) will be used to deliver current to the electrodes to generate tACS resembling theta-gamma PAC[4,10,11]. The impedance of each stimulation electrode will be kept below 10 kΩ. The stimulation waveform will consist of a theta component (5 Hz) delivered at 0.96 mA (1.92 mA peak-to-peak) delivered in a constant sine wave and a gamma component (50 Hz), 3.5 cycles of a sine wave delivered at 0.64 mA (1.28 mA peak-to-peak) superimposed on the theta component and centered on the peak of each cycle. For both tACS and sham conditions, the stimulation will slowly ramp up over the course of 12 s, then the task will begin soon after maximum stimulation output is reached. Stimulation will be maintained at a stable level until the task is complete and the stimulation will ramp down over 12 s. Actual parameters may be varied slightly, but not enough to affect the risk to the participants.

Previous literature suggests that participants are sensitive to stimulation until the sensory neurons in the skin acclimate to the stimulation. Thus, we will use sham stimulation as an active control condition. We will inform our participants that they will sense the stimulation in the skin but will acclimate to the stimulation soon after it begins. They will be informed that they will receive two version of the stimulation, to facilitate blinding in case the participant does not acclimate to the stimulation. For sham, a genuine cross-frequency waveform will be delivered at maximum strength for 12 s, followed by a ramp-down. The ramp-up and ramp-down during the sham stimulation is designed to mimic the feeling of acclimation that is experienced with verum stimulation due to sensory adaptation. Published data from Consultant Frohlich's lab indicate that this procedure provides sufficient participant blinding to the condition[4].

6) *Cognitive Control Task (Emotion Go-NoGo Task*)
Participants will engage in an Emotion Go-NoGo task to activate affective cognitive control during the baseline EEG as well as the stimulation sessions. In this task, participants view facial images exhibiting different emotions (neutral, happy, sad, or angry). For each face (150 ms), they are to press a button within 1500 ms if the face expresses the target emotion (Go trials; 80%) and withhold the response if the face expresses the distractor emotion (NoGo trials; 20%); the pairing of target and distractor emotions vary across blocks. The task includes a total of 640 trials, divided into 8 blocks of 80 trials each. Half (4) of the blocks include original face images (Easy condition), and the other half (4) include visually degraded images (Difficult condition). The two difficulty conditions are presented in alternating order (counter-balanced across participants). Accuracy (particularly on NoGo trials) and reaction time (on Go trials) will be used to index cognitive control behavior as outcome measures. [*Note: the timing and trial parameters of the actual task may be modified slightly depending on initial testing results].

7) *Stimulation Side Effects Questionnaire.* Participants will complete this questionnaire regarding their experience following each stimulation session. They will also be asked to rate how much the stimulation improved cognitive performance as well as if they experienced any side effects (e.g., headache, neck pain, tingling).

8) *Flanker Task.* After completing the Emotion Go-NoGo task, brain stimulation, and Stimulation Side Effect Questionnaire, participants will perform a separate cognitive control task (i.e., Emotional Flanker task). Participants will complete the Emotional Flanker task to evaluate the impact of brain stimulation on cognitive control after stimulation has been completed (i.e., offline effects). Participants will perform a modified Eriksen flanker task in which gray-scaled unpleasant (e.g., injured limbs, barking dog), pleasant (e.g., cute animals, erotic pictures), and neutral stimuli (e.g., lamp, spoon) images from the International Affective Picture System (IAPS) will appear on a computer display. There will be two parts to this task: (1) Unpleasant vs Neutral and (2) Pleasant vs Neutral. Three images will be presented with congruent (e.g., unpleasant - unpleasant - unpleasant) and incongruent (e.g., unpleasant -neutral- unpleasant) conditions. Participants will be instructed to respond by pressing one of two buttons indicating the valence of the central image (i.e., unpleasant versus neutral), while ignoring the adjacent images, and to respond as quickly and accurately as possible. The stimuli will remain on the screen for ~400 ms in the initial block, with an interval of about ~4000 ms between consecutive stimuli. Following a practice block of 30 trials, each participant will complete 10 blocks of 30 trials for a total of 300 trials for each part (Unpleasant vs Neutral and

Pleasant vs Neutral), and a grand total of 600 trials. Performance feedback will be provided and the stimuli presentation time will be adjusted based on performance after each block (e.g., if performance is above 90%, a 40ms shorter presentation time will be used in the next block) to ensure adequate number of errors and consistency in performance across participants within each part. Actual presentation and interval time may differ slightly in implementation from that described above. Estimated to take ~40 minutes. This task is designed to assess error and response monitoring within emotional contexts, which has been shown to be different from monitoring in other contexts, such as emotionally neutral context using arrows. Accuracy and reaction time will be used to index cognitive control behavior as outcome measures. EEG recorded during the Emotional Flanker task will be used to assess neurological indicators of attention control. [*Note: the timing and trial parameters of the actual task may be modified slightly depending on initial testing results. In order to reduce subject burden, experimenters may shorten the task and drop the display of pictures (neutral and valenced), using simple arrow cues instead to indicate a right or left button press].

Follow-up Phone Call (~ 5-10 min)
Approximately 4 weeks (+/- ~7 days) following the completion of Session 3, research staff will call to administer the Stimulation Side Effect Questionnaire as a final safety check and evaluate for any other possible side effects.

Stopping Rules
If a participant reports intolerable discomfort during the tACS procedure, the session will be discontinued. Immediately after each stimulation session ends, participants will complete a tACS side effects questionnaire. A study team member will review the responses and will immediately consult the PI if a participant reports a high (3) to very high (4) rating for any of the side effects rated to be related to the stimulation (4=probable or 5=definite). Subjects may also be withdrawn by the investigator when continued participation would present an unacceptable risk (e.g., worsening symptoms, suicidal thoughts, etc.).

5.3 Participant Compensation

Participants can earn up to $250 if they complete all available procedures in this study:

Session 1 –	$ 45.00
Session 2 –	$ 80.00
Session 3 –	$125.00
TOTAL	$250.00

Participants found to be ineligible after the assessment will be compensated a total of $20 for their time. They will be paid either by gift card or check upon completion of the study. Participants who leave the study before completing all visits will be paid for time.

5.4 **Time and Events Table**

		Session 1	Session 2	Session 3	Follow up Phone call
Procedure	**Pre-Screen**	**Screening & Assessment**	**Week 1**	**Week 2**	**Week 6**
Phone Interview	X				
Informed consent		X			
Pregnancy Screen Attestation		X[1]	X[1]	X[1]	
Demographics/Med History		X	X	X	
Concomitant Meds		X	X	X	
MIRECC GAF		X			
SCID-IV (substance use module only)		X			
YMRS		X	X	X	
HAM-D		X	X	X	
C-SSRS		X	X	X	
BDI		X	X	X	
ASRM		X	X	X	
PSWQ		X	X	X	
BIS		X			
BIS/BAS Scale		X			
Pregnancy Urine Test		X[2]	X[2]	X[2]	
Urine Drug Screen		X[3]	X[3]	X[3]	
Randomization		X			
EEG		X[4]	X[4]	X[4]	
tACS			X[4]	X[4]	
Stimulation Side Effects Questionnaire			X	X	X
Adverse Events Assessment					X

X[1]- Optional if agree to pregnancy test
X[2]- Required if attestation is not signed
X[3]- Required if indicated by verbal report
X[4]- Emotion Go-NoGo Task

6.0 ADVERSE EVENTS

6.1 **Adverse Event Reporting Requirements**

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected after Sessions 2 and 3 through 30 days after study completion. Any serious adverse event that occurs more than 30 days after the last study

Session and is considered related to the study procedure must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline.
- There is satisfactory explanation other than the study procedure for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading, and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the PI to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial study procedure is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE or SAE, as defined in Section 6.2, occurring from the initial study procedure through 30 days following the last Session must be recorded as an adverse event in the subject's source documents and on the clinical research file (CRF) regardless of frequency, severity (grade) or assessed relationship to the study procedure.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the subject begins study procedure is also considered an adverse event. Review of AE and SAE data will be performed and documented on a routine basis by the study team and the PI during weekly study meetings.

6.2 **Definitions**

6.2.1 Adverse Events

Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a subject participating in an investigational study or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

6.2.2 Serious Adverse Event

The study will comply with IRB and FDA reporting requirements and guidelines for SAEs. An adverse event is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- A life-threatening adverse event
  An adverse even is considered 'life-threatening' if, in the view of either the investigator [or sponsor], its occurrence places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization for > 24 hours.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical event
  Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of "Serious Adverse Event." Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

  Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the subject's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

6.2.3 Expected Adverse Events
An adverse event (AE) is considered "expected" in clinical research studies, information on expected adverse events is summarized in the protocol and in the consent document.

6.2.4 Unexpected Adverse Event
An adverse event (AE) is considered "unexpected" if the event is not listed at the specificity or severity that has been observed.

6.3 **Adverse Event Characteristics**

6.3.1 Terms and Grading
The severity or grade of an adverse event may be measured using the following definitions:

Mild: Noticeable to the subject, but does not interfere with subject's expected daily activities, usually does not require additional therapy or intervention, dose reduction, or discontinuation of the study.

Moderate: Interferes with the subject's expected daily activities, may require some additional therapy or intervention but does not require discontinuation of the study.

Severe: Extremely limits to the subject's daily activities and may require discontinuation of study therapy, and/or additional treatment or intervention to resolve and may be life-threatening of fatal.

6.3.2 Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.
Definite – The AE is clearly related to the study treatment/intervention.
Probable – The AE is likely related to the study treatment/intervention.
Possible – The AE may be related to the study treatment/intervention.
Unlikely – The AE is doubtfully related to the study treatment/intervention.
Unrelated – The AE is clearly NOT related to the study treatment/intervention.

6.4 Serious Adverse Event Reporting Guidelines

The PI must be notified within ONE business day of study team's knowledge of any event meeting the criteria and definition of a serious adverse event, regardless of attribution, occurring during the study or within 30 days of the last administration of the study related treatment/intervention.

The investigator must report all events meeting the criteria and definition of a serious adverse event as per the IRBMED reporting guidelines.

6.5 Other Reportable Information or Occurrence (ORIO)

There are types of incidents, experiences, and outcomes that occur during the conduct of human subject research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

Unanticipated problem: Per FDA Procedural Guidance for Clinical Investigators, Sponsors, and IRBs (January 2009), an unanticipated problem is defined as a serious problem that has implications for the conduct of the study (requiring a significant and usually safety-related, change in the protocol (such as revising inclusion/exclusion criteria or including a new monitoring requirement), informed consent or investigator's brochure).

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an ORIO, the investigator should assess the incident and follow IRBMED's reporting guidelines.

6.6 Unblinding Procedures

In the event of any adverse event requiring unblinding, the study staff can be made immediately aware of intervention assignment and the PI will be notified.

7.0 STATISTICAL CONSIDERATIONS

Aim 1 - Acceptability and Tolerability. Neuromodulation studies typically use dropout rate and reported adverse events as measures of acceptability and tolerability, respectively.[12] We will compare the percentage of participants requesting to discontinue the session and the severity of side effects reported following the tACS vs. sham procedure using Bayes factors (BF).

Aim 2 - tACS Effects on Neural Synchrony and Cognitive Control Behavior. EEG data preprocessing and spectral analyses will be conducted using custom MATLAB scripts and EEGLAB following the general methods described in **PI Tso**'s published work.[7] Briefly, data will be downsampled to 500 Hz, filtered (0.1 – 100 Hz), re-referenced to common average, segmented into short epochs (for task data, -400 to 1800 ms time-locked to onset of stimuli; for rest data, 2 s epochs), applied independent component analysis to reject non-neural artifacts, baseline adjusted, followed by automatic artifact rejection of epochs containing voltage exceeding ±100 μV. Data will be mirrored on both ends to minimize edge artifacts, applied Morlet wavelet convolution to extract power of different frequencies from 2 to 60 Hz. Theta-gamma PAC will be computed using the Kullback-Leibler Modulation Index (KLMI)[8] implemented in the PAC Tools plugin for EEGLAB.[9] Neural synchrony (theta-gamma PAC) during the rest EEG blocks and cognitive control performance (sensitivity d', response bias β, and reaction time on the Emotion Go-NoGo task) will be analyzed in separate repeated-measures ANCOVAs, with stimulation (tACS, sham) as within-subjects factor.

Potential Problems & Alternative Strategies

Participants Dropout. The study design entails each participant completing all 3 sessions. Our experience of conducting multiple-session neuromodulation studies suggests that average dropout rate for each subsequent session is 10-15%. We will enroll 30 participants to ensure that at least 20 participants will complete the study even with an overall dropout of 30%.

Statistical Power. For the repeated-measures ANOVAs in Aim 2, assuming a conservative within-subjects correlations of 0.8, a sample size of 20 would provide 80% power at alpha level of .05 to detect small-to-medium within-subjects effect sizes of f=0.21. Although $N = 20$ may not be sufficient to detect smaller effects, our findings will still be useful in providing effect size estimates aiding the sample size calculations for subsequent clinical trials. Additionally, we will use Bayesian methods described in Dr. Tso's publication[15] to estimate the posterior probabilities of beneficial tACS effects. Although the sample will be small, we will also analyze for effects of sex, as the expectation is that we will have 50:50 distribution of male:female.

8.0 DATA AND SAFETY MONITORING PLAN

8.1 Overall framework

Study monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s)

8.2 Roles & responsibilities for regular operations

PI: The PI will meet with study staff on a weekly basis to monitor the progress of the study. During phases when subject recruitment is occurring, the PI will review screenings and scheduling of assessments, as well as strategies to improve recruitment yield at weekly meetings with the study team. Issues such as maintaining confidentiality and privacy of participants during screening,

assessment and data collection, protocol deviations and adverse events will be reviewed. For serious adverse events, the PI will be notified as soon as the SAE comes to the attention of study staff.

Study coordinator/research assistant: This bachelors level individual will carry out the screening and informed consent, and they will provide additional study information, all under the supervision of the PI. The individual will be trained in screening, administering consent and information to the participants. Questions about eligibility will be discussed with the PI. This individual will administer surveys and neuropsychological tests, monitor the participants during the procedure and administer the tACS stimulation. They will receive training in the administration of tACS to ensure they can safely operate the device and are aware of potential side effects. They will conduct any necessary follow-up safety reviews.

Clinical Assessor: Screenings will include thorough assessment of psychiatric health by a masters-level clinician with experience in administration of psychiatric interviews. They will ensure the absence of any neuropsychiatric conditions in the subjects, as well as health conditions that would be a contra-indication to TMS or MRI procedures.

8.3 **Frequency and type of other study monitoring:**

Institutional Review Board monitoring: Approval of all procedures, advertisements and materials given to subjects will be secured from the University of Michigan IRBMED. Annual reviews will be conducted by IRBMED, including the number of subjects screened, enrolled and withdrawn. The IRB will also review protocol deviations, adverse events (according to the reporting timetable of IRBMED) and complaints that arise in connection with the study.

Data monitoring: Data entry will be audited by study staff, who were not involved in primary data entry. Patient questionnaire data will be entered largely through electronic data capture, e.g., REDCap. Research data will be maintained on password protected computers, behind UM firewalls. All enrolled participants will receive participant identifiers, which will be used to code all research records for this project. Paper records with no identifying data beyond the research code are stored in locked cabinets in the PI's office. Copies of executed consent forms will be stored in separate locked cabinets. Demographic data will be entered into spreadsheets, and behavioral data will be merged into files. Password-protected electronic files separated from the research data will track consents, including the link between the research identifier and individual participants. This tracking file will be the sole link between participant identifiers and research data. By deleting the field linking identifiers with participant names, research records can be effectively anonymized.

8.4 **Management of withdrawals and drop-outs:**

When participants drop out during the assessment, but before enrollment, all data including consent form will be destroyed. However, if a participant would agree to be re-contacted for future studies, the consent form will be retained. Limited, de-identified data regarding ethnicity, age, gender, and diagnosis will be retained through the screening process in order to establish the sampling frame. If a participant drops out due to substance use but would otherwise meet the inclusion criteria, all data will be retained until the closing of the project, in case the participant becomes eligible and wishes to be reconsidered for the study before conclusion of recruitment. When participants drop out after

enrollment, data may be destroyed, depending upon the wishes of the participant. However, consent forms and the research number will be retained.

9.0 BENEFITS/RISKS

9.1 **Benefits**

There are no direct benefits from being in this study. However, others may benefit from the knowledge gained from this study as it may lead to better interventions in the future.

9.2 **Risks**

9.2.1 Subject Confidentiality

Measures to protect patient privacy. Study staff will make every effort to limit identifiable information on potential subjects during recruitment. Conversations in which a patient's name must be mentioned, e.g. to determine potential eligibility, will occur in private settings of the clinic. The minimum amount of information will be recorded, and staff are alerted to the dangers of printing, faxing and emailing sensitive information. Phone conversations with potential research subjects will occur behind closed doors, and staff will ask callers if they are in a location where sensitive information can be discussed without danger of revealing confidential information. Any information gathered on subjects who prove ineligible will be destroyed as soon as possible (a list of patients who have declined or screened out will be maintained through the recruitment phase to avoid contacting these subjects again).

9.2.2 Known Potential Risks and Minimization of Risks

(1) Confidentiality risks and Protected Health Information (rare) - Loss of confidentiality around sensitive information such as psychiatric status, history of substance abuse, etc.

Minimization of Risk:

- Investigators and research staff who are responsible for conduct, management, and oversight of the study will be required to fulfill all training requirements for Good Clinical Practice (GCP). All investigators and research staff will be required to handle protected health information as outlined by the Health Insurance Portability and Accountability Act (HIPAA).
- Confidentiality of participant records is assured by assigning a research code and identifying all computer and paper files only by this code, except for a single tracking file. Paper records are kept in locked drawers in a locked room and electronic records are kept on secure server, to which only authorized research personnel have access.
- Screening forms for subjects who do not qualify for the study will be destroyed, except for anonymous information (such as age, gender and education).
- After the completion of data analysis, the record linking subjects to the research codes will be destroyed, thereby anonymizing the data.

(2) Risk of psychological discomfort, stress, or symptom exacerbation (infrequent) - Risks of psychological discomfort associated with the questions asked in the clinical interview or on some of the questionnaires.

Minimization of Risk:

- During the assessment process, subjects are reminded that they do not have to answer questions that make them feel uncomfortable.

- Participants are also reminded during the study that they may choose to terminate participation at any time throughout the study.
- Staff will check in with the participant frequently to if they are alright. Breaks will be offered to reduce any fatigue or stress.

(3) Risk of symptom worsening, suicidal thoughts, plans, and intentions (rare).

Minimization of Risk:

- Clinically trained study staff will be alert for the emergence of new suicidal thoughts amongst enrolled subjects during the course of participation.
- In the event of concerns about suicide risk (revealed during the assessment phase), the PI will be promptly notified, and plans will be formulated for additional emergency evaluation at the psychiatric emergency room (University of Michigan Psychiatric Emergency Services), if appropriate (see Appendix A – MiScanlab Suicide Protocol)

Risks associated with completing the EEG:

(4) Discomfort or anxiety with EEG (infrequent) - The electrode application procedure involves putting gel on your head to help the wires measure brain signals. The gel will seem wet, which some people find slightly uncomfortable. There is also a minor risk of discomfort or anxiety/panic from being in the confined space for the EEG measurement.

Minimization of Risk: Participants can check the EEG measurement equipment and room to check if they will feel comfortable before agreeing to participate. They are also free to stop the study at any time if they become too uncomfortable.

(5) Risk of boredom, fatigue, or discomfort (likely) - It is possible that participants will become fatigued, frustrated, or uncomfortable.

Minimization of Risk: Participants are reminded during the study that they may choose to take a break or terminate participation at any time throughout the study.

Risk associated with tACS:

(6) Risk of Injury and Discomfort (mild and temporary) - The side effects of tACS are mild and transient; the participant may report mild tingling, burning, or itching under the electrode sites.

Minimization of risk:

- To monitor 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.
  If procedure becomes intolerable for the participant, the stimulation will be stopped. They may request a break from the procedures and/or may decline to answer any questions that make them feel uncomfortable.

10.0 QUALITY ASSURANCE AND AUDITS

10.1 **Audits and Inspections**

A regulatory authority (e.g. FDA) may wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the study staff must immediately inform IRB, Medical School Regulatory Affairs, MIAP, etc.

10.2 **Event Windows, Missed Assessments, Missed Sessions and Protocol Deviation Reporting**

Any safety-related assessments (AE Questionnaire, etc.) which are missed will be reported to the IRB as a protocol deviation. For the other assessments, missing assessments will not be reported as protocol deviations unless they constitute > 10% of the total assessments. The time elapsed between the initial assessment and tACS sessions are intended to be approximately 1 week, but scheduling logistics may mean this is not possible for all subjects, and may be longer for some (~ 30 days). These deviations are expected to be minor and will not be reported, although they will be recorded. These allowances should affect neither the scientific integrity nor the safety monitoring provisions of the protocol.

11.0 REGULATORY

11.1 **Institutional Review Board (IRB)**

Before implementing this study, the protocol, the proposed informed consent form and other information to be provided to subjects, must be reviewed and approved by a properly constituted IRB. Any amendments to the protocol must be reviewed and approved by the IRB.

11.2 **Subject Information and Consent**

Study team member will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent will be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it and should be given a copy (electronic or paper form) of the signed document. No subject can enter the study before his/her informed consent has been obtained. The informed consent form is considered to be part of the protocol and will be submitted for IRB approval.

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13.0 APPENDIX

Appendix A – MiScanlab Suicide Protocol

MiSCAN Lab: Suicide Protocol

During normal business hours: page first, call second	Outside normal business hours: call first, page second

To page clinician, go to https://uhmspaging.med.umich.edu/homepaging/PagingSend/search.aspx and submit a clinical page using the appropriate message template:

In-Person	Over-the-Phone*
"SUICIDE PROTOCOL for [Tso/Taylor] study. Participant in RUB [ROOM #]. Call [PHONE#]. – [YOUR NAME]"	**"SUICIDE PROTOCOL for [Tso/Taylor] study. Participant on phone. Call [PHONE #]. – [YOUR NAME]"**

***NOTE FOR POST-COVID REMOTE PHONE SCREENINGS: If you are conducting a phone screen remotely, have the clinician call your cell phone (or the number of whatever phone you used to call the participant). Once the clinician is calling you, tell the participant, "We want to make sure that you are safe, so I am going to have one of our clinicians on the team ask you a few additional questions by having them join our call. Let me place you on brief hold while I add them to the call." Then place the participant on hold (press 'hold and accept call' if using an iPhone), answer the clinician's call, QUICKLY explain the information you collected thus far, and then merge the two calls so you are on a three-way call with the participant. Introduce the participant to the clinician and let the clinician take over from there. You should stay on the line until they are done.**

Chain of Command	
1. Laura Stchur	Cell – (586) 604-0025
2. Stephan Taylor	Pager – 7545 Cell – (734) 717-5413
3. Melvin McInnis	Cell – (734) 355-8803
4. Sarah Sperry	Pager – 25194
5. Cynthia Burton	Pager – 20890 Cell – (714) 393-2978

INSTRUCTIONS BELOW ARE FOR TRAINED CLINICIANS ONLY:

High risk participants → send to PES.
Low-moderate or moderate risk participants → clinician member (NOT study coordinator or undergrad RA) should complete a safety plan with the participant.

IF IN-PERSON: **Clinician and participant should both sign the safety plan. Clinician should make a copy of the safety plan to give to participants and also provide them with the 'UM emergency reference' document on the next page.**

IF OVER-THE-PHONE: Clinician and participant should complete a safety plan over the phone. Be sure to obtain an email address from participant so the coordinator can email them the 'UM emergency reference document.

Suicide Questionnaire

1. Ideation (goal: if and how frequent/serious are the ideas?):

   Have you had thoughts about hurting yourself?
   What kinds of thoughts have you had about killing yourself? (note frequency and duration)

2. Intent (how determined is the person on committing suicide?):
   How do you feel about being suicidal?
   What makes you want to die?
   What do you expect your future to be like?

3. Plan (how well thought out?):
   If you decided to kill yourself, how would you do it?

   3b. Means (can they kill themselves by the above method?):
   e.g. Do you own a gun?

4. Control (what works to help stop the thought?):
   What has kept you from killing yourself before?
   What helps you control your thoughts about wanting to die?

5. Support
   Do you have anyone who keeps you feeling safe?
   Would you like numbers of a hotline, outpatient treatment center, etc…?