Complete Title: Targeting Inter-Hemispheric Alpha Coherence with tACS to Treat PMDD

Short Title: UNC tACS Study

Device Name: XCSITE100 tACS Stimulator

Sponsor: Foundation of Hope for Research and Treatment of Mental Illness

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
MRMD	Menstrually Related Mood Disorder
PMDD	Premenstrual Dysphoric Disorder
tACS	Transcranial Alternating Current Electrical Stimulation
tDCS	Transcranial Direct Current Electrical Stimulation
EEG	Electroencephalography

PROTOCOL SYNOPSIS

Study Title	Targeting Inter-Hemispheric Alpha Coherence with tACS to Treat PMDD
Funder	Foundation of Hope for Research and Treatment of Mental Illness
Clinical Phase	Not Applicable
Study Rationale	Impaired balance in activation between left and right prefrontal cortex has been described in patients with PMDD, consistent with its view as a network disorder. In particular, similar to major depressive disorder, the balance between alpha oscillation power in the left and the right hemisphere is shifted towards the left in patients with PMDD, more so during the luteal phase. We hypothesize that normalization of alpha oscillations in women with PMDD may be accomplished with brain stimulation by application of weak electric currents through transcranial alternating current stimulation (tACS), thereby altering the temporal activity structure of electric signaling in the brain. In this study, we will obtain electroencephalograms (EEGs) to assess whether a single session of tACS will enhance bilateral alpha synchronization (8-12 Hz) (by reducing left prefrontal alpha power) and whether this varies by menstrual cycle phase. An exploratory objective will be to examine the severity of the PMDD symptoms collected daily during the stimulation cycle compared with the baseline cycle.
Study Objective(s)	Primary • To determine whether a single session of tACS will reduce left prefrontal alpha power and thereby restore alpha symmetry Secondary • To determine whether the impact of tACS on alpha power and distribution differs across menstrual cycle phases
Test Article(s) *(If Applicable)*	XCSITE 100 Stimulator The device consists of the following main components/subsystems: 1. Tablet with user interface application (App) 2. Microprocessor 3. Function generator chip 4. Voltage controlled current source 5. Safety circuitry First, the stimulation parameters are specified by the user through the app. The parameters are: 1. tDCS/tACS 2. Number of channels 3. Amplitude 4. Test duration 5. Frequency (for tACS) 6. Password. Next, the parameters are sent via Bluetooth to the microprocessor. The microprocessor interprets these parameters, and programs the function generator chip accordingly through a SPI. The function generator then creates the programmed waveform, which is ultimately a voltage signal. The voltage signal is applied to a voltage controlled current source, which generates the specified amount of current through an arbitrary load resistance.
Study Design	Repeated measure, open-label trial
Subject Population	Inclusion Criteria: · Age 18-52

key criteria for Inclusion and Exclusion:	· Have a prospectively confirmed diagnosis of PMDD · Regularly menstruating without hormonal contraceptives · Medication free or regularly taking medication that has no effect on the nervous system · Not currently pregnant or planning to become pregnant Exclusion Criteria: · Brain surgery or brain implants, including cochlear implants or aneurysm clips · Neurologic disease (e.g. epilepsy or brain tumor) · Traumatic brain injury · Pregnant or nursing · An unstable medical illness (e.g. congestive heart failure or end-stage kidney disease) · History of severe or recurrent substance abuse within 2 years of study enrollment · History of suicidal behavior within 5 years of study enrollment · UNC Department of Psychiatry faculty, employee, or trainee
Number Of Subjects	20
Study Duration	Each subject's participation is expected to last approximately one month. Two tACS with EEG recording sessions will occur, one during the follicular phase (5-9 days after menstruation) and one in the luteal, premenstrual phase (9-13 days after ovulation). Subjects will test their urine at home each morning for approximately one week to determine ovulation. Each tACS/EEG session will last up to 90 minutes. The entire study is expected to last four and a half years
Study Phases Screening Study Treatment	(1) Screening: Subjects with a diagnosis of PMDD confirmed by participation in a PMDD diagnostic study will be screened for eligibility in the tACS Study and review the informed consent forms. (2) Intervention: After consent is obtained, subjects will be asked to notify study personnel when they begin menstruating. If the subject is randomized to receive tACS in the follicular phase first, they will schedule a tACS session within 9 days of the onset of menses. If they are randomized to receive tACS in the luteal phase first, the subjects will then perform a home urine ovulation test every morning until they receive a positive result, at which point they will schedule their tACS session 9-13 days after the positive test result. Each stimulation session will last 40 minutes, plus the time it takes to place electrodes. EEG will be recorded before and after stimulation. At the end of the first session, subjects will be instructed to complete daily symptom rating scales for one completed menstrual cycle, or about 28-32 days. The second tACS session will be identical to the first, except it will occur in the opposite menstrual cycle phase as the first session.
Efficacy Evaluations	Primary efficacy measurement will be changes in left prefrontal alpha power or distribution (asymmetry) following tACS
Pharmacokinetic Evaluations	Not Applicable
Safety Evaluations	Primary measurements that will be used to assess safety:

	• Subject semi-structured interview • Physical symptom items on the Daily Record of Severity of Problems (DRSP)
Statistical And Analytic Plan	We will use a t-test of pre-post changes to examine effects of tACS on left prefrontal alpha oscillations (primary outcome) and differences in effects as function of menstrual cycle phase (secondary outcome). There will be two levels of each of the two repeated within-subjects measures (pre vs post stimulation and follicular vs luteal phase). Order of administration will be assessed by considering order as a between- subjects variable.
DATA AND SAFETY MONITORING PLAN	Previous studies employing tACS, a non-invasive, non-pharmacologic procedure, have shown tACS to be safe and devoid of serious adverse effects. However, tACS does have some mild side effects, such as transient mild tingling, burning, or itching under the electrode sites. In our experience to date, subjects have 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 et al., in preparation). Nonetheless, we will employ the following safety measures: subjects will be told that they can stop the stimulation at any time during the procedure and research personnel present during these sessions will also check in with the subject periodically during the stimulation to see whether they are comfortable.. Each subject will receive a semi-structured interview at the conclusion of the stimulation, and any side effects of greater than mild severity will be reported to the study PI. Possible side effects will be more formally evaluated with the daily rating forms, which will ask the subject to rate physical symptoms such as fatigue, headache, pain as well as any symptoms (which the subject can provide in text in the DRSP). The study coordinator will review the subjects' daily rating forms daily. The PI will review adverse events and side effects in an aggregate format across all subjects enrolled on a quarterly basis. Substantial clinical worsening (compared with the baseline cycles) may result in a subject's discontinuation from the study, at the discretion of the PI. Development of suicidal ideation more than just passive ideation (i.e., sometimes I feel like life is not worth living – not uncommon in women with PMDD in their symptomatic phase) for any reason or any unanticipated serious side effect will result in the subject's discontinuation. Failure of the subject to experience symptom attenuation following the cessation of menses will result in the subject's evaluation, discontinuation from the study, and recommendation of therapeutic intervention if required. The PI is responsible for the assessment and, where appropriate, the reporting of any adverse effects, and the PI can be reached 24/7. Finally, there is a theoretical likelihood that stimulation of neuronal circuits can lead to seizure. However, no studies have reported seizure as a side effect in recent trials of transcranial stimulation for depression or schizophrenia. To further minimize this very small, theoretical likelihood of a seizure, we screen and exclude patients with personal and family history of neurological conditions from the study.

1 BACKGROUND AND RATIONALE

Introduction

Premenstrual Dysphoric Disorder (PMDD) describes the cyclic appearance of affective symptoms and resultant impairment during the luteal phase of the menstrual cycle. The objective of the experiment is to determine if transcranial alternating current electrical stimulation (tACS) will alter prefrontal alpha oscillatory frequencies in women with PMDD, disruption of which has been implicated in other mood disorders. A secondary objective is to determine if menstrual cycle phase will influence the effects of tACS on alpha oscillations. Demonstration of 'target engagement' (alterations in left prefrontal alpha oscillatory frequencies with tACS) is a necessary first step before moving forward with subsequent research that would test whether tACS is a potential treatment for this disorder - promising research in other mood disorders suggests that it may be.

The cause of PMDD is unknown, the morbidity substantial, and the identified treatments limited in their effectiveness, since 40% of PMDD women are non-responders to SSRIs (Yonkers et al. 1997) and many additional women are intolerant of antidepressant induced side effects. PMDD is prevalent (6-8% of women of reproductive age), attended by substantial morbidity, and hence a significant public health problem. Indeed, by World Health Calculations, PMDD is associated with 4.5 million Disability Adjusted Life Years in the US alone (Halbreich et al. 2003). The rationale for testing whether tACS differentially alters target engagement in the follicular versus luteal phases of the menstrual cycle is described below.

Differential Effects on Cortical Activity: The rationale for testing whether tACS differentially alters target engagement in the follicular versus luteal phases of the menstrual cycle is as follows: 1) Role of Hormones: While there is little evidence for ovarian dysfunction in PMDD (Rubinow et al. 1988) a role for the reproductive hormones is clearly implicated, since our own work and that of others has shown that suppression of ovarian function results in a complete remission of symptoms in a majority of women with PMDD, while adding back gonadal hormones results in the return of symptoms in women with PMDD, with no symptoms seen in controls (Schmidt et al. 1998). Both estradiol and progesterone appear capable of precipitating mood destabilization in this paradigm. Recently completed studies from our group further demonstrate that continuous administration of hormones for longer than one-month results in a sustained symptom remission subsequent to the initial precipitated episode. Thus, dysphoric mood states in PMDD appear to be induced by normal changes in gonadal hormones rather than by exposure to elevated hormone levels (i.e., women with PMDD are differentially sensitive to the mood dysregulatory effects of reproductive steroids).

Although there is substantial literature demonstrating the effects of reproductive steroids and, by extension, the menstrual cycle on cortical activity, the usually described effects are disturbed in women with PMDD. Examples include the following: 1) in normal women, activation of the medial orbitofrontal cortex is diminished during the luteal phase and the affective valence of the stimulus to which it responds is reversed (i.e., it responds only to negative stimuli rather than to positive stimuli, as occurs during the follicular phase). These changes are absent in women with PMDD. (Protopopescu et al. 2008) 2) in normal women during the luteal phase, there is an increase in cortical inhibition - a

presumed effect of the GABA receptor activating effects of the progesterone metabolite allopregnanolone. This effect is absent in women with PMDD (Smith et al. 2003). Both animal and human data further suggest the role of a disturbed cortical response to progesterone-derived neurosteroids in PMDD (Epperson et al. 2002; Shen et al. 2007). Thus, sudden changes in the levels of allopregnanolone (as occurs at the start of the luteal phase with increasing levels of progesterone) result in subcortical excitability and irritability in rodents (Shen et al. 2007), while elimination of changes in progesterone-derived neurosteroids (with neurosteroid synthesis inhibition) successfully prevents the emergence of the dysphoric state in PMDD.

Differential Network Activation: Psychiatric disorders characterized by dysregulation of affective state –depression and PMDD - are increasingly recognized as are "network disorders" in which aberrant electric signaling in large-scale neuronal networks mediates the clinical symptoms. Recent studies have documented impaired balance in activation between left and right prefrontal cortex in patients with PMDD (Baehr, Rosenfeld et al. 2004; Accortt, Stewart et al. 2011; Lin, Tsai et al. 2013). In particular, similar to major depressive disorder (Henriques and Davidson 1990), the balance between alpha oscillation power in the left and the right hemisphere is shifted towards the left in patients with PMDD. The presence of alpha oscillations corresponds to a relative decrease in neuronal activity (inverse relationship). Therefore, such a left-shifted alpha asymmetry is indicative of hypoactivation of the left hemisphere – a common finding in imaging studies of patients with MDD (Grimm, Beck et al. 2008). Since this asymmetry is exacerbated during the luteal but not the follicular phase (corresponding to the time course of symptom presentation in PMDD, (Baehr, Rosenfeld et al. 2004; Lin, Tsai et al. 2013), we hypothesize that successful normalization of alpha oscillations in women with PMDD would be a plausible approach to symptom remediation. This network level intervention can be accomplished with brain stimulation by application of weak electric currents, a non-invasive approach to modulating intrinsic cortical network dynamics. The advantage of this approach is twofold: it is non-pharmacologic and thus avoids the otherwise attendant side effects; and it will provide systems level insights into the pathophysiology underlying mood state dysregulation.

Brain stimulation by constant electric currents applied to the scalp (tDCs) modulates neuronal excitability in humans (Wagner, Valero-Cabre et al. 2007; Zaghi, Acar et al. 2010; Stagg and Nitsche 2011). Transcranial current stimulation with sine-wave stimulation waveforms (transcranial alternating current stimulation, tACS) likely enhances cortical oscillations in a frequency specific manner. The mechanisms of weak electric fields generated by tDCS and tACS previously have been demonstrated to interact with cortical network activity by altering the temporal activity structure of electric signaling in cortex (Frohlich and McCormick 2010; Ali, Sellers et al. 2013). In this study, we will assess whether tACS will decrease left frontal alpha power (8-12 Hz) and whether the extent of the decrease varies by menstrual cycle phase. An exploratory objective will be to examine the severity of the PMDD symptoms collected daily during the stimulation cycle and compare that severity with baseline symptoms ratings collected during the PMDD diagnostic study from which these participants will be recruited. The rationale for this stimulation is the known deficits in the overall structure of cortical activity in this frequency band in patients with mood disorders (Henriques and Davidson 1990; Baehr, Rosenfeld et al. 2004; Bruder, Sedoruk et al. 2008; Accortt, Stewart et al.

2011; Lin, Tsai et al. 2013) and the previously demonstrate clinical benefits of tDCS in the treatment of mood disorders (Berlim, Van den Eynde et al. 2013; Brunoni, Valiengo et al. 2013). In this study, we will use more targeted stimulation waveforms by employing bilateral tACS instead of tDCS. We hypothesize that this choice of a more sophisticated waveform that directly enhances synchronization between the two hemispheres may be more effective in engaging the target. tDCS modulates overall activity levels of the targeted cortical area in a non-specific manner. Here, however, we propose to evaluate a more specific stimulation modality, tACS, (10 Hz stimulation frequency) that has been shown to selectively enhance cortical alpha rhythms (Neuling et al. 2013). Since the selected patient population reportedly exhibits specific deficits in the alpha frequency band, our stimulation approach will provide a more targeted and therefore possibly a more effective manipulation.

Protocol History: This protocol was originally designed to test the therapeutic efficacy of tACS in PMDD in a double blind, randomized, sham controlled, cross-over study of 5 tACS sessions. We were unable to recruit subjects, largely consequent to the many daily treatment sessions required. We subsequently changed the primary focus of the study to that of determining whether a single session of tACS engaged left prefrontal cortical alpha oscillations and, by reducing them, reduced alpha asymmetry. We further asked whether this effect was menstrual cycle phase-dependent. If target engagement was demonstrated, we then intended to perform a follow-up study to assess clinical efficacy, particularly but not exclusively if there were any evidence for reduction of mood symptoms on the exploratory analysis.

Name and Description of Investigational Product or Intervention

XCSITE100 Stimulator

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

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

The stimulator has two main components:

1. Android tablet with user interface application (i.e., App)
2. Stimulator with:
    a. Microprocessor

b. Function generator chip
c. Voltage controlled current source
d. Safety circuitry

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

1.1 Non-Clinical and Clinical Study Findings

Potential Benefits: Research is designed to benefit society by gaining new knowledge. This study is not designed to benefit participants. Affective disorders are prevalent and representative an enormous public health burden. This study offers the general benefit of advancing our understanding of the brain circuitry that may be altered by the menstrual cycle in women with PMDD. In other ongoing studies, our results show enhanced alpha oscillations by tACS in patients with schizophrenia or depression, with associated decreased hallucinations in the former and depressive symptoms in the latter.

Risk/Benefit Assessment: Transcranial current stimulation has been used in hundreds of studies without any reports of serious side-effects (Brunoni and Amadera 2011). In our experience to date in studies of patients with schizophrenia and with depression, no serious adverse events have been reported. Therefore, transcranial current stimulation represents an extremely safe and non-invasive therapeutic approach.

Passing weak electric current through the scalp is also routinely done for measuring electrode resistance in all EEG recordings, a known safe procedure. Importantly, this stimulation mode has nothing to do with electroconvulsive therapy, which applies many orders of magnitude higher stimulation current. Rather, transcranial current stimulation is so weak that it does not produce super-threshold activation of neurons (Frohlich and McCormick 2010). There is a rare/theoretical likelihood that stimulation of neuronal circuits can lead to seizure. However, no studies have reported seizure as a side effect in recent trials of tDCS for depression or schizophrenia (Brunelin et al., 2012; Berlim et al. 2013) (nor in any trials to date). To further minimize this very small, theoretical likelihood of a seizure, we screen and exclude patients with personal and family history of neurological conditions from the study.

When comparing input of energy into the subject, both the amount of current and the area over which this current is dispersed are critically important. The value of interest is called the current density, which is the amount of current divided by the area. Our stimulation area is 25 cm2. Therefore, we will use this device at 2mA, resulting in a current density of 0.08mA/cm2. Our use of this transcranial current stimulation device poses 'minimal risk' to subjects because of the low current density being applied. Our application of current will result in an equivalent current density as performed in prior studies, in which subjects experienced no serious side-effects or harm. Prior studies using other brain stimulators have used a range of current densities: (Iyer, Mattu et al. 2005) used a maximum current density 0.08mA/cm2, conducted at NINDS with DC stimulators, and (Groppa, Bergmann et al. 2010) used a maximum current density of 0.125mA/cm2 with no reported side effects

With use of this technology, some subjects report transient tingling underneath the electrode on the scalp, itching, headache, burning sensation, and discomfort. However, a recent meta-review has

failed to find any significant difference in occurrence rates between transcranial current stimulation and sham control itching (39.3% vs. 32.9%, p>0.05), tingling (22.2% vs. 18.3%, p>0.05), headache (14.8% vs. 16.2%, p>0.05), burning sensation (8.7% vs. 10%, p>0.05) and discomfort (10.4% vs. 13.4%, p>0.05)). (Brunoni, Amadera et al. 2011). In our experience, increased sleepiness and flickering lights were more common than sham stimulation. During stimulation, the research assistant will ask the subject about her comfort level. If the subject reports any pain, stimulation will immediately be stopped.

EEG: EEG is a commonly used measure and is not associated with adverse events. Individuals may find the electrode gel annoying, as hair will require shampooing after the conclusion of the EEG.
Embarrassment: Self-report assessments contain questions regarding sensitive personal information. This risk is necessary to assess mood symptoms and psychopathology. Subjects will be assured upon intake that only study personnel will see associated DRSP responses.

Confidentiality breach: A breach of confidentiality could indicate to others a participant's history of PMDD. Risk of breach of confidentiality is minimized by identifying research subjects by a study number on all research documents. Study documents that must contain personal information, including the informed consent document will be kept in filing cabinets in locked rooms. The document that links study ID number to personal identifying information will be kept electronically on a UNC password protected server. All data will be stored in locked cabinets inside locked offices. Electronic data will be stored only on password-protected computers, and data encryption methods will be used during communication between investigators. Only study personnel will have access to these data. All study staff participate in annual human subject training that includes education about responsibilities to the minimize risk of confidentiality breach.

1.4 Relevant Literature and Data

There is a growing literature on the use of tACS to understand the role of brain oscillations in behavior, cognition, and memory (see references Negahbani**).** Brain stimulation by constant electric currents applied to the scalp (tDCs) modulates neuronal excitability in humans (Wagner, Valero-Cabre et al. 2007; Zaghi, Acar et al. 2010; Stagg and Nitsche 2011). Transcranial current stimulation with sine-wave stimulation waveforms (transcranial alternating current stimulation, tACS) likely enhances cortical oscillations in a frequency specific manner. The mechanisms of weak electric fields generated by tDCS and tACS previously have been demonstrated to interact with cortical network activity by altering the temporal activity structure of electric signaling in cortex (Frohlich and McCormick 2010; Ali, Sellers et al. 2013).

The rationale for this stimulation is the known deficits in the overall structure of cortical activity in this frequency band in patients with mood disorders (Henriques and Davidson 1990; Baehr, Rosenfeld et al. 2004; Bruder, Sedoruk et al. 2008; Accortt, Stewart et al. 2011; Lin, Tsai et al. 2013) and the previously demonstrate clinical benefits of tDCS in the treatment of mood disorders (Berlim, Van den Eynde et al. 2013; Brunoni, Valiengo et al. 2013). Patients with MDD exhibit elevated oscillatory activity in the alpha band (8-12Hz), which is often localized to left frontal regions, resulting what has been called “frontal alpha asymmetry.” (Leucher, Cook, et al. 2012; Henriques and Davidson 1990).

In this study, we will use more targeted stimulation waveforms by employing bilateral tACS instead of tDCS. We hypothesize that this choice of a more sophisticated waveform that directly enhances synchronization between the two hemispheres may be more effective in engaging the target. tDCS modulates overall activity levels of the targeted cortical area in a non-specific manner. Here, however, we propose to evaluate a more specific stimulation modality, tACS, (10 Hz stimulation frequency) that has been shown to selectively enhance cortical alpha rhythms (Neuling et al. 2013). Since the selected patient population reportedly exhibits specific deficits in the alpha frequency band, our stimulation approach will provide a more targeted and therefore possibly a more effective manipulation.

Mood ratings in this study will be obtained with the DRSP (Endicott et al. 2006). This rating scale is among the most widely used for assessment of symptoms of PMDD (and their requisite change in severity over the course of the menstrual cycle).

2 STUDY OBJECTIVES

The purpose of this study is to determine in women with PMDD whether a single session of tACS will alter left prefrontal alpha oscillatory power (enhance bifrontal symmetry, which is described as abnormal in PMDD). The secondary objective will be to determine if this 'target engagement' will differ by menstrual cycle phase. Our exploratory objective will be to examine whether changes in cortical dynamics will be associated with symptom reduction relative to baseline, pre-stimulation levels (obtained in the diagnostic feeder protocol IRB# 05-3000).

2.1 Primary Objective

2.1.1 To determine whether a single session of tACS in women with PMDD decreases left prefrontal alpha power, ascertained by comparing EEG prior and subsequent to tACS.

2.1.2 To determine whether a single session of tACS will alter prefrontal alpha symmetry

2.2 Secondary Objective

2.2.1 Determine whether the impact of tACS on left alpha power differs across menstrual cycle phases by comparing primary outcome measures obtained in the follicular vs the luteal phase of the menstrual cycle.

3 INVESTIGATIONAL PLAN

3.1 Study Design

Repeated measure, open-label study design.

Overview of study phases:

- **Screening/Baseline:** subjects will be followed for three months in a related protocol to document that subjects meet criteria for PMDD, showing affective symptoms of requisite severity as present during the luteal phase and relatively absent during the follicular phase.
- **Intervention/Treatment**: a single 40-minute session of tACS, administered once each in the follicular and luteal phases of the menstrual cycle

- **Follow up:** subjects will be followed with daily ratings until completion of the menstrual cycle following the second tACS. Any subject endorsing suicidal ideation, severe deterioration of mood, or distressing somatic symptoms on daily rating forms will be referred to Dr. Rubinow for acute evaluation and determination of appropriate subsequent clinical response.
- **Unscheduled Visits:** not applicable

3.2 Allocation to Treatment Groups and Blinding (if applicable): Not applicable

3.3 Study Duration, Enrollment and Number of Subjects

The study is anticipated to last five years. After being shown as eligible (in our screening protocol), subjects will sign an informed consent form and be deemed as enrolled when they have participated in the first tACS session. We will enroll 22 subjects to accommodate a 10% drop-out and achieve a sample size of 20. Each subject's participation is expected to last approximately one month. Two tACS sessions with pre-post EEG recordings will occur, one during the follicular phase (5-9 days after menstruation) and one in the luteal, premenstrual phase (9-13 days after ovulation). Subjects will test their urine at home each morning for approximately one week to determine ovulation. Each tACS/EEG session will last up to 90 minutes. There will be approximately 20 people in this research study.

3.4 Study Population

-Inclusion and Exclusion Criteria

Subjects will be women with PMDD. All subjects will have had their diagnoses confirmed by participation in our diagnostic study. The diagnosis requires demonstration of at least a 30% increase in symptom ratings in the seven days preceding menses compared with the seven days following the cessation of menses in two of three menstrual cycles.

In addition to PMDD diagnosis, all women enrolled must also meet the following criteria:
Inclusion Criteria:

- Age 18-52
- Have participated in our PMDD diagnostic study
- Regularly menstruating without hormonal contraceptives (e.g., birth control pills, injections, implants, progestin IUDs)
- Medication free or regularly taking medication that has no effect on the nervous system
- Not currently pregnant or planning to become pregnant
- With sufficient resource to prevent pregnancy

Exclusion Criteria:

- Brain surgery or brain implants (e.g., cochlear implants or aneurysm clips)
- Neurologic disease (e.g., epilepsy or a brain tumor)
- Traumatic brain injury
- Pregnant or nursing
- Any unstable medical illness (e.g., congestive heart failure or end-stage kidney disease)
- History of severe or recurrent substance use disorder, or any substance abuse within 2 years of study enrollment
- History of suicidal behavior within 5 years of study enrollment
- UNC Psychiatry faculty, employee, or trainee
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4 STUDY PROCEDURES

- tACS administered on two
- High density EEG recording before and after each tACS administration
- Daily Record of Severity of Problems (DRSP) ratings daily throughout the study administered electronically via Qualtrics survey platform. This 20-item self-report rating scale assesses physical and mood symptoms that accompany ovarian hormone changes and is often used as a dimensional measure of PMDD.

4.1 Screening/Baseline Visit procedures

Effect of Menstrual Phase on Target Engagement

Diagnostic/Baseline Phase: We will attempt to recruit subjects whose PMDD status has been confirmed in our screening protocol (diagnostic study). Using the DRSP (Daily Record of Severity of Problems), subjects must show symptom severity of 4 or greater (scale range 1-6) for two days on a core emotional symptom in the luteal phase, absence of symptom severity during the follicular phase, and a 30% or greater increase in severity of symptoms in the 7 days preceding menses with 7 days following the end of menses. For those who meet criteria, we will describe the tACS study during their last visit in the diagnostic (screening) study. It will be during this in person visit that interested subjects would review the consent form and we would confirm eligibility for the tACS study. Consequently, no separate recruitment materials or phone screening materials are required for this study as all women will be recruited from the diagnostic study. After consent is provided, subjects will be asked to call and notify the study staff when they begin menstruating. If the subject is randomized to receive tACS in the follicular phase first, they will schedule a tACS session within 9 days of the onset of menses. If they are randomized to receive tACS in the luteal phase first, the subjects will then perform a home urine ovulation test every morning until they receive a positive result, at which point they can schedule their tACS session 9 - 13 days after the positive test result.

Transcranial Current Stimulation: Subjects will report for bilateral stimulation with tACS (one session) per menstrual phase, over the course of one menstrual cycle (unless it is an anovulatory cycle, in which case the participant will be asked to conduct the ovulation testing for one additional cycle). Each participant will receive tACS once in the follicular cycle phase and once in the luteal cycle phase, in counterbalanced order. The tACS stimulation will deliver a maximum amplitude of 2mA for a total of 40 minutes of stimulation per session. Electrodes will be saline soaked, 5x5cm, and placed over F3 and F4 locations to target dorsolateral prefrontal cortex. The return electrode will be located over CZ. A transcranial current stimulator designed by the Frohlich lab (XCSITE 100 stimulator) will be used. After the first tACS session, participants will be instructed to begin daily mood ratings as recorded in the Daily Record of Severity of Problems. This 20-item self-report rating scale assesses physical and mood symptoms that accompany ovarian hormone changes and is often used as a dimensional measure of PMDD.

Electroencephalography (EEG): Each EEG session will last 8 minutes, and participants will alternate between having eyes open and closed at 2-minute intervals. A total of four EEG recordings will be performed throughout participation; two recordings per menstrual phase to be collected before and after stimulation. EEG will be recorded with a standard Nicolet v32

clinical EEG machine that is approved for clinical use and that has been used in all previous studies by the Frohlich Lab. Briefly, 10mm gold cup electrodes are fitted to the individual participants for brief, non-invasive recordings of brain activity.

4.2 Intervention/Treatment procedures (by visits)

Effect of Menstrual Phase on Target Engagement

Transcranial Current Stimulation: Subjects will report for bilateral stimulation with tACS (one session) per menstrual phase, over the course of one menstrual cycle (unless it is an anovulatory cycle, in which case the participant will be asked to conduct the ovulation testing for one additional cycle). Each participant will receive tACS once in the follicular cycle phase and once in the luteal cycle phase, in counterbalanced order. The tACS stimulation will deliver a maximum amplitude of 2mA for a total of 40 minutes of stimulation per session. Electrodes will be saline soaked, 5x5cm, and placed over F3 and F4 locations to target dorsolateral prefrontal cortex. The return electrode will be located over CZ. A transcranial current stimulator designed by the Frohlich lab (XCSITE100 stimulator) will be used. After the first tACS session, participants will be instructed to begin daily mood ratings as recorded in the Daily Record of Severity of Problems via electronic Qualtrics survey. This 20-item self-report rating scale assesses physical and mood symptoms that accompany ovarian hormone changes and is often used as a dimensional measure of PMDD.

Electroencephalography (EEG): Each EEG session will last 8 minutes, and participants will alternate between having eyes open and closed at 2-minute intervals. A total of four EEG recordings will be performed throughout participation; two recordings per menstrual phase to be collected before and after stimulation. EEG will be recorded with a standard Nicolet v32 clinical EEG machine that is approved for clinical use and that has been used in all previous studies by the Frohlich Lab. Briefly, 10mm gold cup electrodes are fitted to the individual participants for brief, non-invasive recordings of brain activity.

4.3 Follow- up procedures (by visits): Will be scheduled only as necessary to assess acute suicidal ideation, severe mood deterioration, or severe somatic symptoms**.**

4.4 Unscheduled visits: not applicable

4.5 Concomitant Medication documentation: not applicable

4.6 Rescue medication administration (if applicable)

4.7 Subject Completion/ Withdrawal procedures: While extremely unlikely, any subject who becomes pregnant or who experiences a seizure during this study will be withdrawn. Any subject who experiences an acute worsening of mood or appearance of suicidal ideation will be assessed by the PI and may be withdrawn from the study. Subjects will be compensated monetarily for time and effort. For mileage subjects will be reimbursed 34 cents/mile. Compensation structure is as follows:

Participants will be paid $40 per each tACS stimulation study visit, and an additional $25 upon completion of the Daily Rating Forms. Total: $105 per subject

Subjects will be paid at the end of their participation. If a subject is withdrawn by the investigators or withdraws herself, she will be compensated for participation up to the point of withdrawal.

4.8 **Screen failure procedures:** As potential subjects will have been identified as appropriate through the related diagnostic screening protocol, we do not anticipate screening failures. In the case that a subject enrolls to participate in the trial but does not meet criteria, the study coordinator completing the screening process will clearly explain why the subject does not meet criteria. However, in the case that a subject does not qualify based on acute suicide risk, Dr. Rubinow will evaluate the subject and determine the appropriate clinical intervention.

5 STUDY EVALUATIONS AND MEASUREMENTS

- **List variables that will be abstracted from medical charts –** not applicable
- **Describe baseline evaluation –**

  1) Prior to enrollment in the tACS study, subjects must meet diagnostic criteria for PMDD. The DRSP (Daily Record of Severity of Problems), a validated daily symptom chart widely used for the diagnosis of PMDD, includes 21 items grouped into 11 domains that address the criterion of symptoms in PMDD (depression, anxiety, lability, anger, interest in activities, concentration, lethargy, appetite, sleep, control, and physical symptom). Each item is rated on a scale of 1 ("note at all") to 6 ("extreme"). Using the DRSP, subjects must show symptom severity of 4 or greater for two days on a core emotional symptom in the luteal phase, absence of symptom severity during the follicular phase, and a 30% or greater increase in severity of symptoms in the 7 days preceding menses with 7 days following the end of menses.

  2) left prefrontal alpha power prior to tACS, obtained with EEG

  Describe how measurements will be taken.

  1) symptom measures are self-reported on DRSP via Qualtrics survey tool; 2) EEG will be obtained for 8 minutes, with two-minute alternating intervals of eyes open and eyes closed.

- **Describe rating scales, tests, psychological tools, laboratory evaluations, etc.**

  1) Resting state EEG (RSEEG) recordings will be completed at several times during the course of the study. Subjects will complete an alternating eyes open/eyes closed RSEEG immediately before and after the 40 minutes of stimulation. This measure is used to determine the immediate after-effects of tACS on brain activity, specifically on alpha oscillation power, as well as how consecutive stimulation sessions may affect these after-effects.

  2) DRSP - Daily Record of Severity of Problems (DRSP) ratings daily throughout the study administered electronically via Qualtrics survey platform. This 20-item self-report rating scale assesses physical and mood symptoms that accompany ovarian hormone changes and is often used as a dimensional measure of PMDD.

5.1 **Efficacy Evaluation (if applicable):** Comparison of left prefrontal alpha power in post-tACS EEG compared with that preceding the procedure; comparison of degree of change in prefrontal alpha in follicular vs luteal phase.

5.2 **Pharmacokinetic Evaluation:** Not applicable

5.3 **Safety Evaluations -** Previous studies employing tACS, a non-invasive pharmacologic procedure, have shown tACS to be safe and without adverse effects. Nonetheless, the study coordinator will review the subject's daily rating forms on a daily basis. Subjects experiencing a worsening of mood symptoms, the failure of mood symptoms to improve following menses, or the appearance of active suicidal ideation

will be immediately referred to the PI, who will evaluate the subject and decide whether acute treatment is required. The PI will also review adverse events and side effects in an aggregate format across all subjects enrolled on a quarterly basis.

6 STATISTICAL CONSIDERATION

This is repeated, single intervention (tACS) administered during the follicular and luteal phase. Change in left prefrontal alpha power on EEG is the primary outcomes. Effect of menstrual cycle phase is the secondary outcome. We plan to analyze our data using a repeated measure analysis of variance (ANOVA-R), with two within subject variables, each with two levels: time (pre vs post tACS), and menstrual cycle phase (follicular vs luteal). We will assess any effects of order of administration (follicular first vs luteal first) by including order as a between-subjects variable.

Clinical symptoms will be quantified as the mean of daily nighttime ratings (individual symptoms rated from 1 to 6) collected in the follicular (days 4 – 9) and luteal phases (the 6 days preceding menses) as recorded in the DRSP.

Decrease in left prefrontal power (reflection of reduction in alpha asymmetry) will be calculated by comparing results from the following time points: 1) immediately before the stimulation and 2) immediately following the stimulation in each of the follicular and luteal phases.

The main intent of this study is to conduct a pilot study, the results of which could be used in a larger trial that is appropriately powered for efficacy. Nonetheless, we intend to determine whether tACS influences alpha coherence on EEG. Due to the novelty of the application and the treatment strategy, we do not have all the required parameters to estimate the power for the repeated measure design on alpha coherence on EEG. However, the primary purpose is to demonstrate tACS associated changes in alpha coherence and whether that differs by cycle phase. The aim to demonstrate 'target engagement' does not necessarily lend itself to traditional power calculations and we will rely on Dr. Frohlich's extensive experience with analyzing these data. In his experience, he is confident that if, in fact, if there are menstrual cycle differences in alpha coherence, 20 participants will be sufficient to demonstrate that effect.

6.1 Primary Endpoint

Change in Alpha Frequency Electrical Activity in Left Frontal Cortex from Stimulation [Time Frame: 8-minute recording before vs after intervention]

6.2 Secondary Endpoint

Difference in magnitude of effect of tACS on left prefrontal alpha in follicular vs luteal phase.

6.3 Statistical Methods

Baseline Data: alpha oscillations in left frontal cortex before stimulation; severity of luteal phase symptoms in screening DRSP.

Efficacy Analysis: This is repeated, single intervention (tACS) administered during the follicular and luteal phase. Change in left prefrontal alpha power on EEG is the primary outcome. Effect of menstrual cycle phase is the secondary outcome. We will use a t-test of pre-post changes to examine effects of tACS on left prefrontal alpha oscillations (primary outcome) and differences in effects as function of menstrual cycle phase (secondary outcome). There will be two levels of each of the two repeated within-subjects measures (pre vs post stimulation and follicular vs luteal phase). Order of administration will be assessed by considering order as a between- subjects variable.

Exploratory analysis: Assessment of possible changes in mood will be assessed with linear mixed model regression analysis comparing mean luteal phase core affective symptoms (depression, irritability) after stimulation with means during baseline.

Pharmacokinetic Analysis (if applicable): not applicable

Safety Analysis - The PI will review any adverse effects and will quarterly review aggregated data, which will be recorded descriptively. Safety/ Tolerability will be assessed in two ways: 1) with somatic symptoms contained within the DRSP, completed daily, and with symptoms reviewed daily by the research coordinator. Any symptoms of moderate or greater severity appearing proximate to the tACS session will be reported to the PI. 2) with a semi-structured interview at the end of each tACS session, inquiring about possible side effects during the procedure (e.g., tingling, flickering lights, itching, burning sensation, headache, neck pain, scalp pain). Side effects of moderate or greater severity will be reported to the PI, who will also review aggregate data at the end of the experiment.

6.4 Sample Size and Power - The main intent of this study is to conduct a pilot study, the results of which could be used in a larger trial that is appropriately powered for efficacy. Nonetheless, we intend to determine whether tACS influences alpha coherence on EEG. Due to the novelty of the application, we do not have all the required parameters to estimate the power for the repeated measure design on alpha coherence on EEG. However, the primary purpose is to demonstrate tACS associated changes in alpha coherence and whether that differs by cycle phase. The aim to demonstrate 'target engagement' does not necessarily lend itself to traditional power calculations and we will rely on Dr. Frohlich's extensive experience with analyzing these data. In his experience, he is confident that if, in fact, if there are menstrual cycle differences in alpha coherence, 20 participants will be sufficient to demonstrate that effect.

Due to the novelty of the application, we do not have all the required parameters to estimate the power for the repeated measure design on alpha coherence on EEG. Nonetheless, preliminary data from a study of five tACS sessions in a study of patients with major depression showed a significant alteration in left frontal alpha power following 10Hz stimulation in a sample of 10 subjects ($p<.05$, paired t-test with FDR correction). Notably, there was no significant difference between results after one and five sessions. As such, we are confident that a sample size of 20 should enable us to establish target engagement as well as determine whether there are meaningful menstrual cycle differences in alpha coherence.

6.5 Interim Analysis

Other than the quarterly review of safety data, no formal interim analysis is planned.

7 STUDY INTERVENTION

Device Description: XCSITE100 Stimulator

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

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

The stimulator has two main components:

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

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

SAFETY FEATURES

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

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

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

1. AUTOMATIC SOFTWARE CURRENT CUTOFF. The output of the current sensor described above is read by a microprocessor, which compares the reading to a value of ±3 mA peak. If the current exceeds these limits, stimulation is stopped, a relay in series with the electrode is opened, and the power supply used for stimulation is turned off. The user is then given the option to investigate the issue , and cancel or resume the test. Since high-side current sensing is used (described above), any short circuit of the electrode terminals to ground will be detected.

2. AUTOMATIC HARDWARE CURRENT CUTOFF. The output of the current sensor is fed into a pair of comparators which detect if the current exceeds ±4.5 mA. If so, the fault is latched such that the relay in series with the electrodes is opened. Additionally, the microprocessor is notified of this instance through an interrupt. Upon this interrupt, the microprocessor immediately stops stimulation and the power supply used for stimulation is turned off.

3. PERMANENT HARDWARE CURRENT CUTOFF. A 5 mA fast-acting fuse is in series with the electrode connector. If the above two over-current detection methods fail, the fuse will below, and the stimulator will no longer be electronically connected to the device.

4. POWER SUPPLY FUSE. Finally, if for no other reason the entire device draws too much current, the main power supply fuse is blown. This fuse is sized with a cutoff of 200% of steady-state operating current.

8 STUDY INTERVENTION ADMINISTRATION (if applicable)

- **Randomization procedures -** A random number table will be used to assign the first tACS session to either the follicular or luteal phase.
- **Blinding procedures –** not applicable
- **Unblinding procedures** not applicable

9 SAFETY MANAGEMENT

Previous studies employing tACS, a non-invasive, non-pharmacologic procedure, have shown tACS to be safe and devoid of adverse effects. Nonetheless, the study coordinator will review the subjects' daily rating forms daily. The PI will review adverse events and side effects in an aggregate format across all subjects enrolled on a quarterly basis. Substantial clinical worsening (compared with the baseline cycles) may result in a subject's discontinuation from the study, at the discretion of the PI. Development of suicidal ideation more than just passive ideation (i.e., sometimes I feel like life is not worth living – not uncommon in women with PMDD in their symptomatic phase) for any reason or any unanticipated serious side effect will result in the subject's discontinuation. Failure of the subject to experience symptom attenuation following the cessation of menses will result in the subject's evaluation, discontinuation from the study, and recommendation of therapeutic intervention if required. If there are unanticipated serious adverse events or side effects, the information will be provided to the UNC Biomedical IRB for recommendation regarding the continuation or termination of the study. No seizures have been reported with administration of tACS or tDCS. Nonetheless, Dr. Bradley Vaugh, Department of Neurology, has agreed to be available should any untoward event occur.

DATA AND SAFETY MONITORING PLAN

The NIH policy on Data and Safety Monitoring stipulates that, in most studies, the PI would be expected to perform some monitoring functions as part of the general oversight and scientific leadership of the study. This is the strategy that we intend to employ in the proposed research according to the following data and safety monitoring plans:

I. Grading of adverse events (AEs)

We will employ the grading scale adopted by the UNC IRB to grade and report AEs. Adverse events will be classified according to severity as either mild, moderate, or severe.

Mild AE: is defined as having no effect on activities of daily living, such as transient lightheadedness or sweating with venipuncture; headache; mild skin irritation; or something of equal significance that requires no medical intervention and is of marginal clinical relevance.

Moderate AE: would be associated with temporary (minutes to a few days) disruption in activities of daily living, such as temporary loss of consciousness with venipuncture; worsening of migraines or headache that require bed rest; an increase in depressive symptoms; dizziness that precludes ambulation; or something of equal significance.

Severe AE: would include any event that acutely threatens the patient's health, is life-threatening, or potentially permanently disabling, or an event of equal significance.

II. Monitoring and reporting of adverse events (AEs)

The study coordinator and tACS technician will monitor side effects during and following tACS administration. Side effects consistent with moderate or severe AEs will be immediately reported to Dr. Rubinow, who will be responsible for determining the next course of action, which might include discontinuation of the subject from the study. Dr. Rubinow will review aggregate reports of side effects/AEs quarterly. As the contact PI, Dr. Rubinow will be the one responsible to report all AEs reported as moderate or severe to the IRB and CTRC within one week.

10 DATA COLLECTION AND MANAGMENT

Daily Record of Severity of Problems (DRSP) responses will be collected using study ID number as the identifier, stored by Qualtrics survey software and will be monitored to ensure consistency and completion of responses. Symptom ratings will be used for safety during the study..

EEG recordings will be kept on a secure server within the Department of Psychiatry and will be analyzed by Dr. Frohlich.

Participants will be identified by study ID number on all research documents and in electronic data files. All data will be stored in locked cabinets inside locked offices, and electronic data will be stored only on password-protected file servers only accessible from computers in the Psychiatry Department. Only study personnel will have access to these data. Qualtrics will be used to collect self-report questionnaire data for all participants. Participants will not enter any personally identifying information into the Qualtrics system, and they will be identified by their unique study ID only.

The document that associates subject names and study ID numbers will be destroyed 5 years following the last publication to come from the study. Consent forms and any other documentation containing subject information other than study ID will be destroyed at this time as well. Paper documentation will be shredded, and computerized data will be permanently deleted from the lab server. Subject names and contact information will be maintained indefinitely for the purpose of future studies and stored in a secure, password-protected database that meets UNC standards for data security as determined by department IT security specialists.

11 RECRUITMENT STRATEGY

Potential subjects will have already identified themselves by participating in our diagnostic study. Subjects who will enter the experiment will be those women who demonstrate the presence of PMDD, defined by the demonstration with daily mood ratings of a 30% or more increase in mean affective symptom ratings in the seven days prior to menses (luteal phase) compared with ratings during the seven days following the cessation of menses (follicular phase).

Based on when potential subjects are first identified as meeting criteria, they will either be recruited (and screened) at the second visit of the diagnostic feeder study, or they will be contacted by phone and re-screened via telephone interview. Given that the exclusion criteria for both the feeder study and this study are similar, the re-screening process is simply used to confirm that nothing has changed since they participated in the feeder study.

12 CONSENT PROCESS

The study coordinator or other study staff will obtain informed consent from individuals during their second visit in the diagnostic feeder protocol. During the consenting process, all the applicable consent forms will be reviewed with each individual, who will be given as much time as she would like to decide whether to participate and have any questions answered. Additionally, during the discussion of consent forms, potential subjects are asked at the end of each section of the consent whether they understand what was described and whether they have any questions. Potential subjects will also be offered the chance to ask questions directly to the investigators.

13 PLANS FOR PUBLICATION: Upon completion of study, data will be analyzed and submitted for publication in an appropriate journal.

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