Lupus Brain: Transcranial Alternating Current Stimulation (tACS) to Target the Neurophysiology of Depression, Cognitive Deficits, and Pain in patients with Systemic Lupus Erythematosus (SLE)

NCT number NCT04141046
Document Date 03/04/2022

Lupus Brain: Transcranial Alternating Current Stimulation (tACS) to Target the Neurophysiology of Depression, Cognitive Deficits, and Pain in patients with Systemic Lupus Erythematosus (SLE)

Principal Investigators: Saira Sheikh, MD; Flavio Frohlich, PhD

Co-Investigators: Crystal Schiller, PhD; Yueh Lee, MD, PhD

Version: 1.8
4 March 2022

Summary of Changes from Previous Version:

Affected Section (s)	Summary of Revisions Made	Rationale
1.2.2, 1.2, 1.3, 4.1, 8.1.3, 10.3	Replacement of SCID with MINI	Shorter and more applicable in remote settings
1.2, 1.2.2 1.3, **8.2.3, 10.1.3 10.3**	Removal of BDNF saliva collection and mention of genetic testing	This was built into the initial protocol as an exploratory hypothesis prior to the COVID 19 pandemic. Given the current climate of the pandemic, we have decided that this poses unnecessary risk and would therefore like to remove it from the protocol. This also eliminates the only potential genetic testing that was built into the protocol.
8.1.5	Removal of Bartonella questionnaire	We have already removed the Bartonella blood draw but did not remove the related questionnaire until now
5.1, 6.4	Updating and clarifying inclusion criteria to state no changes to SLE or psychiatric	Non-SLE related and non-psychiatric med changes should not confound analysis of study intervention

	meds 4 weeks prior to screening instead of all meds 6 weeks prior	
8.3.2	CTCAE Version 5.0 Published: November 27th, 2017	Updated to clarify version being used

Table of Contents

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

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

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

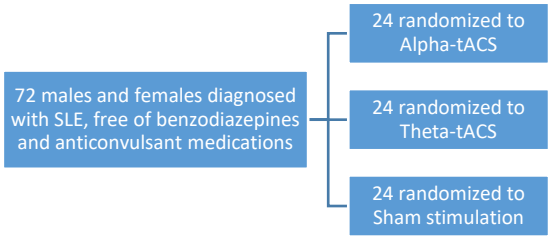
Title:	Lupus Brain: Transcranial Alternating Current Stimulation (tACS) to Target the Neurophysiology of Depression, Cognitive Deficits, and Pain
Study Description:	The purpose of this clinical trial is to investigate the effects of non-invasive transcranial alternating current stimulation (tACS) on patients diagnosed with lupus. We will recruit up to 72 males and non-pregnant females diagnosed with systemic lupus erythematosus (or lupus) and a diagnosis of depression. At the initial session, consent will be obtained and eligibility will be determined. Eligible participants will undergo a structural MRI as part of the screening process, then be randomized and have 5 consecutive daily, 40 minute stimulation sessions. Participants will be randomly assigned to one of three groups: sham stimulation, individualized alpha-tACS (usually 8-12 Hz), or individualized theta-tACS (individualized alpha frequency minus 4 Hz). Participation will include 1 to 11 visits. Neurophysiological measures will be taken before and after the stimulation sessions on the first and fifth days of the intervention, as well as the 2-week follow-up and 4-week follow-up visits. Psychiatric clinical assessments will be performed at baseline (Day 1 of stimulation), Day 5 of stimulation, and at both follow-up visits using the HDRS17, the Hamilton Anxiety Rating Scale (HAM-A), the Inventory of Depression and Anxiety Symptoms (IDAS), and the Comparative Pain Scale Chart. Participants will also be asked to complete self-report surveys via REDCap at a 3-month time point measured from completion of the intervention.
Objectives:	*Primary Objective:* To investigate the physiological changes in patients with systemic lupus erythematosus over the course of a 5-day, 40-minute stimulation protocol, specifically changes in alpha oscillation power from resting-state EEG recordings from baseline (Day 1) to Day 5 of stimulation. *Secondary Objectives:* To elucidate the relationship between changes in EEG and changes in depression and pain symptoms, by comparing the changes in symptoms and the change in alpha oscillation power over the course of the intervention (baseline to day 5 of stimulation).
Study Population:	We will recruit up to 72 males and non-pregnant females aged 18-65 with a diagnosis of lupus, free of benzodiazepines and anticonvulsant medications. We anticipate having evaluable data from at least 45 participants. Participants will be recruited in person from the UNC Rheumatology Specialty Clinic and through indirect recruitment from the surrounding Chapel Hill, Durham, and Raleigh areas.
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	University of North Carolina at Chapel Hill

Description of Study Intervention:	Patients will be randomized with equal allocation into 3 study arms: an active sham, individualized alpha-tACS (usually 8-12 Hz), or individualized theta-tACS (individualized alpha frequency minus 4 Hz). Active sham treatment will include 20 seconds of ramp in to 40 seconds of 10Hz tACS with a ramp out of 20 seconds for a total of 80 seconds of stimulation. The choice of an active sham is motivated to enhance success of patient blinding by mimicking skin sensations associated with tACS. alpha-tACS and theta-tACS will also have a 20 second ramp in and ramp out with 40 minutes of stimulation for a total of 2440 seconds. Stimulation waveforms are sine-waves with an amplitude of 1mA zero-to-peak. Participants will stay in a relaxed yet experimentally controlled state by watching a nature movie such as "Reefscape" during stimulation.
Study Duration:	2 years
Participant Duration:	Eligible participants who complete this clinical trial will have a total of 9 to 11 visits; an initial screening session, a visit for a structural MRI to screening for incidental findings and to aid signal processing of EEG data, 5 days of stimulation, a 2 and a 4 week follow up visit (follow up sessions are measured from completion of the intervention). Participants will also be asked to complete self-report surveys via REDCap at a 3-month time point measured from completion of the intervention. Study visits include clinical assessments, patient questionnaires/surveys, neuropsychological assessments, and specimen collection including up to 2 blood draws. The initial session will take approximately 3 hours, each blood draw will take 30 minutes (and will be included in other visits when possible), the first and last day of stimulation will take approximately 5 hours. Days 2 through 4 of stimulation will take 2 hours each day. The visit for the structural MRI takes approximately 45 minutes. The 2-week follow up will take approximately 3 hours and the 4-week follow up will take approximately 4 hours. The 3-month surveys will take approximately an hour. We estimate that total participation to be approximately 28 hours.
Funding:	The Fund for Excellence in Lupus and Sjogren's

1.2 SCHEMA

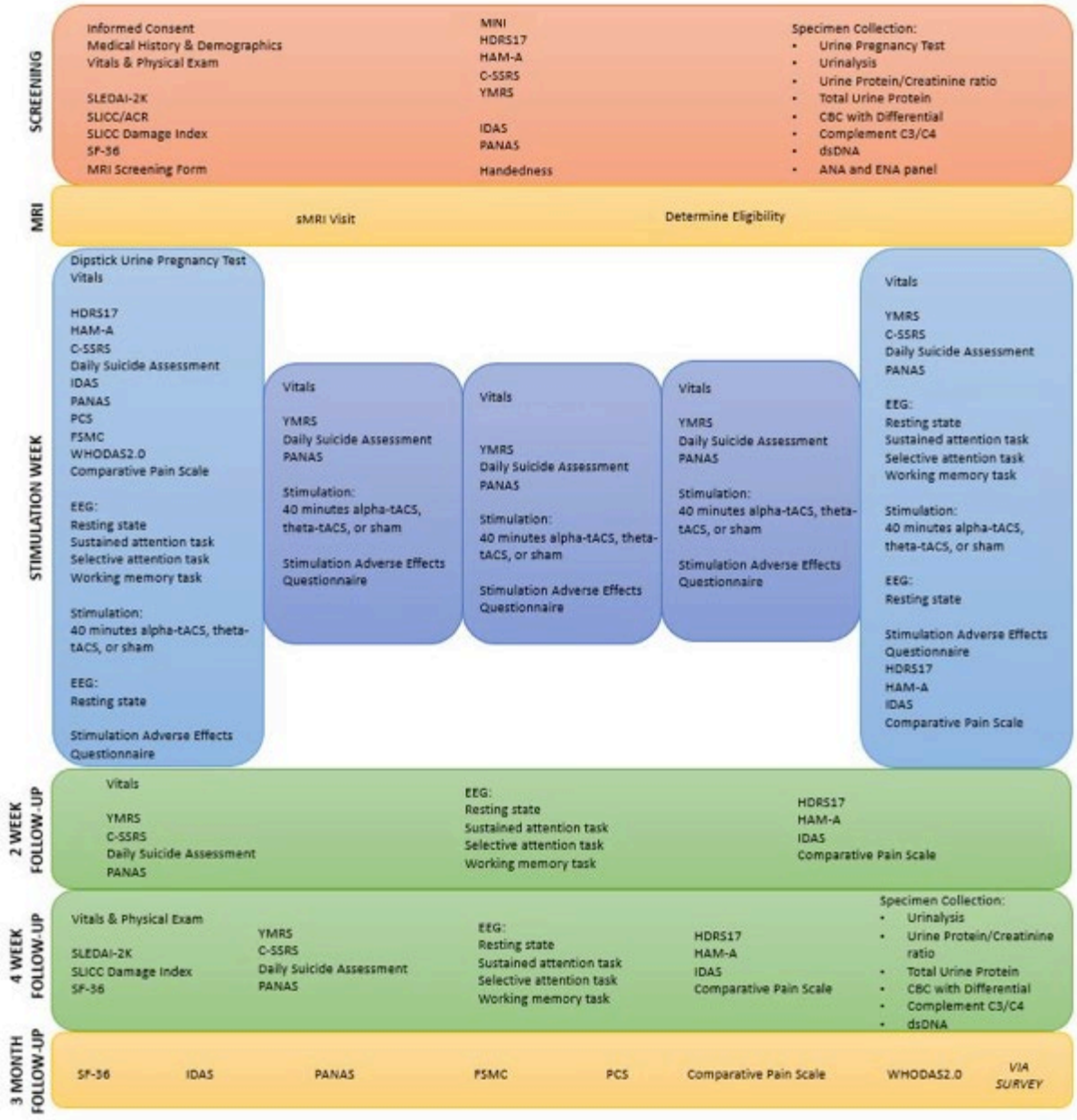
1.2.1 ARM ALLOCATION

Up to 72 participants will be equally randomized in to one of three arms (1:1:1):



**Randomization is double-blind

1.2.2 STUDY LAYOUT



*Note: Follow-up weeks are counted from the completion of the intervention

**Note: Prior to the week of stimulation, participants will return for a structural MRI to assist with source localization in EEG and screen for incidental findings.

Abbreviations:

- American College of Rheumatology (ACR)
- Antinuclear Antibody test (ANA)
- Anti-double stranded DNA (anti-dsDNA)
- Complete Blood Count (CBC)
- C-reactive protein (CRP)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Electroencephalogram (EEG)
- Extractable Nuclear Antigen Antibodies (ENA)
- Fatigue Scale for Motor and Cognitive Functions (FSMC)
- Hamilton Anxiety Rating Scale (HAM-A)
- Hamilton Depression Rating Scale, 17 item (HDRS17)
- Inventory of Depression and Anxiety Symptoms (IDAS)
- Magnetic Resonance Imaging (MRI)
- Mini International Neuropsychiatric Interview (MINI)
- Polymerase Chain Reaction (PCR)
- Positive and Negative Affect Schedule (PANAS)
- Pain Catastrophizing Scale (PCS)
- Resting state EEG (RSEEG)
- Short Form Health Survey (SF-36)
- Structural Magnetic Resonance Imaging (sMRI)
- Systemic Lupus Erythematosus (SLE)
- Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)
- Systemic Lupus Collaborating Clinics (SLICC)
- Transcranial alternating current stimulation (tACS)
- WHO Disability Assessment Schedule 2.0 (WHODAS 2.0)

- Young Mania Rating Scale (YMRS)

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	**Screening (Initial Session & MRI)**	**Day 1 of Stimulation (Baseline)**	**Days 2 of Stimulation**	**Day 3 of Stimulation**	**Day 4 of Stimulation**	**Day 5 of Stimulation**	**2 Week Follow-Up**	**4 Week Follow-Up**	**3 Month Follow-Up**
Visit Windows (in days)	**- 14 to 0**	**1**	**2**	**3**	**4**	**5**	**19 +/- 3**	**33 +/- 3**	**93 +/- 3**
Informed Consent[4]	X								
MRI Screening Form	X								
sMRI[3] & Neuroradiologist review	X								
Determine Eligibility	X								
Pregnancy Test	X	X							
MINI[4]	X								
Handedness[4]	X								
Randomization		X							
Suicide assessment[4]		X	X	X	X	X	X	X	
C-SSRS[4]	X	X				X	X	X	
YMRS[4]	X	X				X	X	X	
HDRS17[4]	X	X				X	X	X	
WHODAS 2.0[4]		X							X
HAM-A[4]	X	X				X	X	X	
IDAS[4]	X	X				X	X	X	X
PANAS[4]	X	X	X	X	X	X	X	X	X
Comparative Pain Scale[4]		X				X	X	X	X
PCS[4]		X				X	X	X	X
FSMC[4]		X				X	X	X	X
RSEEG		X				X	X	X	
Sustained attention task		X				X	X	X	
Selective attention task		X				X	X	X	
Working memory task		X				X	X	X	
Blinding Assessment						X			

Stimulation (alpha-tACS, theta-tACS, or sham)		X	X	X	X	X			
Stimulation Side Effects Questionnaire		X	X	X	X	X			
SLE Requirements									
Medical History and Demographics[4]	X								
Physical Exam (Height and Weight)	X							X	
Vital Signs	X	X	X	X	X	X	X	X	
Subject Assessments									
SLICC/ACR SLE Criteria[4]	X								
SLEDAI-2K[1]	X							X*	
SF-36[4]	X							X	
SLICC Damage Index[4]	X							X	
Blood Draw for Laboratory Assessments (UNC McClendon Lab)									
CBC with Differential	X							X	
Urinalysis	X							X	
Urine protein/creatinine ratio	X							X	
Complement C3/C4	X							X	
Anti-dsDNA	X							X	
ANA[2]	X								
ENA panel[2]	X								
CRP	X							X	

[1]A SLEDAI-2K assessment will not be conducted at the 4 week follow-up if this visit occurs within 30 days or less of the Screening Initial Session.

[2] ANA and ENA panel labs will only be completed if there are no recorded historical values in participant's medical chart.

[3]sMRI will be completed if a patient has not undergone a MRI in the past 3 months prior to screening. Reference section 5.4 for additional detail.

[4]Patient consenting, medical history collection, and SLE indices (SLICC/ACR SLE Criteria, SLEDAI-2K, SLICC Damage Index) will be offered to be completed remotely through UNC's REDCap platform. Patient self-reported questionnaires will also be conducted using REDCap's secure survey function. Patient self-reported questionnaires include: CPS, PCS, SF-36, WHODAS2.0, PANAS, and FSMC. Patient assessments include: MINI , HDRS17, HAM-A, C-SSRS, Suicide Assessment, YMRS, will be offered both in-person and remotely. Remote clinical assessments will be conducted over the phone or UNC approved video platform and will be recorded at the approval of the participant. All remote activities will adhere to the statement of activities listed above and windows to be completed.

2 INTRODUCTION

2.1 STUDY RATIONALE

Systemic lupus erythematosus (SLE) is a severe, chronic autoimmune disorder that affects multiple organ systems and is characterized by a pro-inflammatory effect (Azizoddin et al., 2018). It is not uncommon for patients with SLE to also have several comorbidities, including depression, chronic pain, and cognitive impairment (i.e., "brain fog"). Previous research shows that these comorbidities have the strongest association with quality of life metrics, demonstrating that alleviation may lead to better quality of life (Mackay, 2015). Current treatments for SLE are inadequate and the development of new pharmacological therapies has been slow (Dall'Era et al., 2019), indicating the need for more targeted therapies.

2.2 BACKGROUND

Mood disorders are the second most frequent neuropsychiatric (NP) manifestation observed in SLE occurring in up to 20% of SLE patients (de Amorim et al., 2019). These symptoms may occur simultaneously or independently of other clinical indications which negatively affect quality of life. Common SLE treatment options such as corticosteroids may be associated with the exacerbation of NP symptoms such as mood disorders. Furthermore, suicidal ideation has also been observed in up to 25% of SLE patients and lifetime mood disorders emerged as a significant risk factor (de Amorim et al., 2019).

The experience of pain involves multiple areas of the brain, including the somatosensory and prefrontal cortices, as well as several subcortical areas (Ploner, Sorg, & Gross, 2017). Chronic pain can result in abnormal neuronal oscillatory activity, including decreased peak alpha frequency (Pinheiro et al., 2016). Targeted stimulation modalities, such as transcranial alternating current stimulation (tACS), can directly engage and modulate oscillatory activity, which would result in symptom changes. tACS utilizes sine-wave stimulation waveforms that can enhance specific oscillatory activities (Pinheiro et al., 2016) (Herrmann, Rach, Neuling, & Strüber, 2013). In fact, tACS at the alpha frequency can alter the experience of pain in induced pain paradigms (Arendsen, Hugh-Jones, & Lloyd, 2018), as well as directly target and enhance alpha oscillatory activity over the somatosensory cortex in patients with chronic low back pain (Ahn, Prim, Alexander, McCulloch, & Frohlich, 2019).

Furthermore, Cognitive impairment is observed in 20–60% of SLE patients when standard testing is performed (de Amorim et al., 2019). The American College of Rheumatology (ACR) defines cognitive dysfunction as significant deficits in any or all of the following cognitive functions: simple or complex attention, reasoning, executive skills, memory, visual-spatial processing, language, and psychomotor speed.

Targeting depression in patients with SLE may provide benefit to these patients, as there is a clear relationship between chronic pain and depression (Tunks, Crook, & Weir, 2008). Both depression and chronic pain can result in cognitive impairment (Gotlib & Joormann, 2010). In our previous trial of tACS to target alpha oscillations in the somatosensory cortex (Ahn et al., 2019), we found a relationship between the subjective experience of pain and alpha power over the somatosensory cortex, indicating that alpha activity can determine how someone experiences their pain. Furthermore, we found that tACS enhanced alpha oscillations over this same region, resulting in decreased experience of pain. We have also previously targeted frontal alpha oscillations near the somatosensory cortex in patients with depression, resulting in clinical improvement and target engagement of alpha oscillations (Alexander et al., 2019). We propose that the same stimulation montage that was previously used in depression could be beneficial to patients with SLE, resulting in reduced depression symptoms, thus resulting in reduced chronic pain and cognitive difficulties.

We propose a 3-arm (tACS at alpha frequency, tACS at theta frequency, and sham stimulation) clinical trial to assess the use of tACS to treat depression in patients with SLE. As described in our previous study (Alexander et al., 2019), we will use alpha-tACS to directly target alpha oscillations and reduce depression symptoms. Previous research in our lab has found that alpha oscillations exist in an antagonistic relationship with theta oscillations (Stitt, Zhou, Radtke-Schuller, & Frohlich, 2018), which is why we choose to include the individualized theta-tACS as a possible mechanism to engage alpha oscillations and potentially treat depression more effectively than alpha-tACS. Furthermore, the choice to include a frequency control is to ensure that stimulation is *frequency*-dependent, rather than *stimulation*-dependent (i.e., that target engagement and therapeutic efficacy is different between the two stimulation frequencies). Safety concerns are paramount in a depressed population, which is why we have chosen to include daily questionnaires of safety and will exclude participants at risk of suicide, as well as employ a DSMB to monitor any safety issues that may arise.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risk of Confidentiality Breach: In the unlikely event of a breach of confidentiality, people might discover that an individual was involved in this research study. This is especially sensitive because the population recruited for this study may be subjected to negative consequences caused by the stigma of diagnosis. Furthermore, some might not agree with the principle of participating in research or of changing natural brain activity. To avoid breaches in confidentiality, study documents that contain personal information, including the informed consent document, and the document that links study ID numbers to personal identifying information are kept in locked filing cabinets in locked rooms, separate from any source documents containing participant dummy identifiers. All data is stored in locked cabinets inside locked offices; electronic data will be stored only on password-protected computers, and data encryption

methods will be used during communication between investigators. Only study personnel will have access to these data. All study staff participate in annual human participant training that includes education about responsibilities to the minimize risk of confidentiality breach. For remote assessments conducted via UNC approved video platform or phone, sessions may be recorded. Clinical interviews will be recorded with the participant's permission for the sole purpose of reviewing symptoms with other trained researchers to reach a consensus on diagnoses. No personally identifying information will be included in the recordings. Like all other data, they will be identified by a code number and kept on a password protected computer.. Audio and video recordings may be requested to be turned off at any time.

Risk of Embarrassment: Self-report assessments contain questions regarding sensitive personal information. This risk is necessary in order to assess mood symptoms, self-report pain, and associated psychopathology. Participants will be assured upon intake that only study personnel will see any clinical information.

Risk of Injury and Discomfort: The side effects of tACS are mild and transient; in fact, low intensity transcranial current stimulation, such as tACS, has been used for several years without any report of serious side effects (Frohlich & McCormick, 2010). Furthermore, this stimulation mode has nothing to do with electroconvulsive therapy that applies many orders of magnitude higher stimulation current. Rather, transcranial current stimulation is so weak that it does not cause super-threshold activation of neurons (Khan, Khan, Shankles, & Polissar, 2002). However, tACS does have some mild side effects, such as transient mild tingling, burning, or itching under the electrode sites. In the first part of this study, participants from all three groups 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., 2019). In order to monitor these, we will be administering an adverse effects 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 adverse effects questionnaire or by self-report), the stimulation will be immediately stopped.

Risks associated with emotional distress in case of incidental findings on structural MRI or a false positive pregnancy test.

Risks associated with venous blood draw include minimal discomfort and/or bruising. Infection, excess bleeding, clotting, and fainting are also possible, although unlikely.

Patients experiencing depression have a higher risk of suicide. We have no evidence that our treatment paradigms will in any way increase this likelihood. In a similar study in patients with major depressive disorder (MDD), 4 participants in the sham/placebo stimulation group experienced an increase in suicidal thoughts and only one of those 4 participants reported suicidal intent. No participants who

received tACS reported an increase in suicidal ideation from baseline. We will be using the Suicide Item included in the HDRS17 to assess suicide risk. Inclusion criteria states that the patient must be low suicide risk defined as a score of less than 3 on the HDRS17 suicide item, potential participants that have an above "low risk" designation will not be eligible for the study. Additionally, we will administer this as a daily questionnaire to assess suicide risk. In the case suicide risk increases after the screening visit, the participant will be asked to stop the study and will be provided with a referral to UNC Psychiatry and their mental health care or family medical doctor will be contacted. Dr. Schiller, Co-I, will facilitate this process.

Research within our lab has shown that alpha and theta oscillations exist in an antagonistic relationship. Therefore, an increase in alpha oscillations would result in a decrease in theta oscillations (and vice versa). In a previous tACS trial (Alexander et al., 2019), we found that alpha-tACS reduced alpha oscillations over the course of 5 days. We propose that alpha-tACS did this through synchronization of those two areas. Theta-tACS would theoretically work in an orthogonal mechanism to alpha-tACS, by suppressing alpha oscillations, rather than synchronizing it. Theoretically, theta-tACS could exacerbate underlying depression and worsen outcomes. Furthermore, traditional treatments for depression (e.g., antidepressants) run the risk of exacerbating depression symptoms as well. We will be following patients closely throughout the study as well as employ the assistance of a Data Safety and Monitoring Board, which we plan to review our blinded data every 6 months.

2.3.2 KNOWN POTENTIAL BENEFITS

Our novel approach of non-invasive brain stimulation as a treatment for neurological illnesses has the potential to treat symptoms not only in depression and chronic pain, but also in schizophrenia, and anxiety disorders.

This study has not been designed to benefit the individual participants. However, participants in this study may experience some degree of relief from the side effects of SLE (such as depression, chronic pain, and cognitive impairment) as a result of tACS intervention. There are no serious risks to the participant from the treatment used in this study. The chance to understand and develop a new treatment for a wide range of psychiatric disorders is an important step in helping the millions of people in the world who suffer from mental illness.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risks and benefits presented above are no more serious than for other clinical trials in this population. Based on the need for complementary and alternative treatments for SLE, the potential risks are worth the potential benefits.

3 OBJECTIVES AND OUTCOME MEASURES

OBJECTIVES	OUTCOME MEASURES	JUSTIFICATION
Primary		
To investigate the physiological changes in patients with systemic lupus erythematosus over the course of a 5-day, 40-minute stimulation protocol, specifically changes in alpha oscillation power from resting-state EEG recordings from baseline (Day 1) to Day 5 of stimulation.	Resting state EEG recordings taken on Day 1 and Day 5 of stimulation.	The protocol is for a 5-day intervention. The primary objective is focused on looking at the change in brain activity over the course of the intervention. Long-term effects (2-week follow-up and 4-week follow-up) will be assessed as exploratory outcomes.
Secondary		
To elucidate the relationship between changes in EEG and changes in pain and depression symptoms, by comparing the changes in symptoms and the change in alpha oscillation power over the course of the intervention (baseline to day 5 of stimulation). The SF-36 will be evaluated at screening and 4-week follow-up.	Correlations between clinical assessments and alpha oscillation power (as measured by resting state EEG recordings) from Day 1 and Day 5 of stimulation.	The objective is to target engagement (i.e., if the stimulation paradigm changes brain activity); the secondary objective is to determine if this engagement resulted in behavioral changes.
Exploratory		
To investigate the outlasting effects, if any, of tACS on brain activity and clinical assessments.	Resting state EEG recordings taken on 2-week and 4-week follow up visits.	The objective is to explore if any changes in brain activity persist as long-term effects. Long-term effects are detected at the 2-week and 4-week follow ups.
To investigate whether tACS increases cognitive control signals during cognitive tasks that probe sustained attention, selective attention, and working memory.	Correlations between frontal midline alpha and theta activity (as measured from EEG recordings on D1, D5, 2-week, and 4-week follow up visits) and accuracy at cognitive	We hypothesize that tACS will improve cognitive control. In particular, we hypothesize that alpha frequency tACS will improve performance the most for tasks that require attention (sustained attention and selective attention tasks),

OBJECTIVES	OUTCOME MEASURES	JUSTIFICATION
	tasks (reaction time for attention tasks, accuracy for working memory task).	whereas theta frequency tACS will improve performance the most for the working memory task.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The design for this study is a pilot, randomized, double-blind, sham-controlled clinical trial which will be used to investigate the effects of alpha-tACS on patients with systemic lupus erythematosus (SLE), as well as determine the relationship between physiological changes and clinical changes. We are recruiting from a clinical population. For this trial, we are seeking up to 72 males and non-pregnant females, ages 18-65, with a diagnosis of SLE, free of benzodiazepines and anticonvulsant medication, and at a low risk for suicide according to the Hamilton Depression Rating Scale (HDRS17). We anticipate having evaluable data from at least 45 participants. All women of child-bearing potential will be asked to take a pregnancy test during the initial session in order to determine eligibility for the study; nursing or pregnant participants will be excluded from participation and all women of child-bearing potential will be required to use an appropriate form of birth control throughout their participation. These individuals will be outpatients and may seek mental health care from a family practitioner, therapist or psychiatrist.

This is a single-site, pilot clinical trial with 3 arms of equal allocation (1:1:1). We estimate 2 years to complete study enrollment. Participants will be randomly assigned to one of three arms; active sham stimulation, individualized alpha-tACS (usually 8-12Hz), or individualized theta-tACS (alpha frequency minus 4 Hz). Active sham stimulation will include 20 seconds of ramp-in to 40 seconds of 10 Hz tACS with a ramp out of 20 seconds for a total of 80 seconds of stimulation. The choice of an active sham is motivated to enhance success of patient blinding by mimicking skin sensations associated with tACS. Alpha- tACS and theta-tACS will have a 20 second ramp-in and ramp-out with 40 minutes of stimulation for a total of 2440 seconds of stimulation. Stimulation waveform is a sine-wave with an amplitude of 1 mA. In each arm, participants will stay in a relaxed and yet controlled state by watching a nature movie such as “Reefscape” during stimulation.

Eligible participants who complete this clinical trial will have a total of 9-11 visits; including an initial screening session, 5 days of stimulation, a visit for a structural MRI, a 2 and a 4 week follow up visit (follow up sessions are measured from end of stimulation). Participants will also be asked to complete self-report surveys via REDCap at a 3-month time point measured from completion of the intervention. The initial session will take approximately 3 hours, each blood draw will take 30 minutes (and will be included in other visits when possible), the first and last day of stimulation will take approximately 5 hours. Days 2 through 4 of stimulation will take 2 hours each day. The visit for the structural MRI takes approximately 45 minutes. The 2-week follow up will take approximately 3 hours and the 4-week follow up will take approximately 4 hours. The 3-month surveys will take approximately an hour. We estimate that total participation to be approximately 28 hours.

If a participant is unable to complete his/her blood draws during the indicated sessions, there may be an additional 2 sessions.

As this study requires several days of participation in a row, we will allow participants to miss one stimulation session, as long as it is made up at the end of the stimulation week. In addition, follow-up sessions will be permitted to be scheduled ± 3 days to account for possible scheduling problems.

Our primary objective is to investigate the physiological changes in patients with SLE over the course of a 5-day, 40-minute stimulation protocol, specifically changes in alpha oscillation power from resting state EEG recordings over the course of the intervention (Day 1 to Day 5 of stimulation). As a secondary objective, we are looking to elucidate the relationship between changes in EEG and changes in clinical assays.

In the light of COVID-19, we will offer participants the option to consent and conduct patient self-reported questionnaires and patient assessments remotely to protect our high-risk patient population. This option will continue throughout the remainder of the study. Self-reported questionnaires and SLE indices detailed in the schedule of activities will be done using REDCap's secure survey function. All study staff has been vaccinated against COVID-19.

Patient assessments will be conducted using a UNC approved virtual platform. Participants will meet with the study coordinator on the phone or through a UNC approved video platform to conduct the following assessments: MINI , HDRS17, HAM-A, C-SSRS, Suicide Assessment, and YMRS. Sessions will be recorded only using audio and stored on a password protected computer until we are able to score and validate the assessments. All optional remote procedures have been noted in the schedule of assessments.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study is a double-blind, randomized, sham-controlled interventional study. The choice of double-blind and randomized for this study is important for the integrity of our data, especially for the clinical assessments. All individuals involved with data collection (as well as all randomized participants) will not know participant assignment until all data has been collected. This will reduce implicit and explicit bias in the data collection process.

In this study, participants will be randomized in to one of three arms: active sham/placebo stimulation, individualized alpha-tACS (usually 8-12Hz), or individualized theta-tACS (alpha frequency minus 4 Hz). We propose that alpha-tACS will be the therapeutic frequency, based on work in our lab demonstrating the effect of 10Hz-tACS on depression (Alexander et al., 2019) and chronic pain (Ahn et al., 2019); whereas, previous work from our lab demonstrates that alpha oscillations exist in an antagonistic relationship with theta oscillations (Stitt et al., 2018). Therefore, theta-tACS was chosen as a control stimulation frequency for this study.

In this design, our sham/placebo stimulation is active, including 80 seconds of stimulation (20 seconds ramp-in to 40 seconds of 10 Hz tACS at 1 mA with 20 seconds of ramp-out). This choice of active sham/placebo is important to mimic the skin sensations and other transient side effects associated with stimulation. Typically, stimulation side effects only last approximately a minute into stimulation; indicating that theoretically sham/placebo stimulation should be difficult to differentiate from verum tACS.

4.3 JUSTIFICATION FOR DOSE

In a previous study at the Carolina Center for Neurostimulation, we utilized a 5-day, 40-minute stimulation paradigm to treat the mood symptoms of patients with major depressive disorder (MDD) (Alexander et al., 2019). In this study, we found that 10Hz-tACS selectively modulated alpha power as measured by changes in resting state EEG, which resulted in changes in clinical outcomes. As we are looking for long-term changes similar to this previous study, we are choosing to follow the same protocol in patients with SLE.

4.4 END OF STUDY DEFINITION

The end of this study is defined as when the last participant completes the 3 month follow up survey. In this case, we anticipate having evaluable data from at least 45 participants; therefore, enrollment will discontinue when 45 participants have completed the entire study duration including the 3-month follow up.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

- Ages 18-65 years
- Meet the 2012 Systemic Lupus International Collaborating Clinics criteria OR the 1997 American College of Rheumatology criteria for SLE diagnosis, including testing positive ANA and/or anti-dsDNA and/or anti-ENA
- Low suicide risk (score of <3 on the Suicide Item on the HDRS17)
- Capacity to understand all relevant risks and potential benefits of the study (informed consent)
- Not experiencing manic episode; a manic episode is defined as a score > 12 on the YMRS.
- Stable on all SLE-related and psychiatric meds for 4 weeks prior to screening

5.2 EXCLUSION CRITERIA

- Drug-induced SLE and any other rheumatologic or autoimmune disease (except for Sjogren's syndrome and mixed connective tissue disease)
- Positive hepatitis B surface antigen or hepatitis C antibody or HIV antibody/antigen in medical history, as patients with these illnesses cause also experience depression and cognitive impairment (from the illness itself or the treatment) that may not be mitigated by tACS, thus confounding the results.
- Have received intravenous glucocorticoids at a dosage of ≥ 500mg daily within the past month
- Opportunistic infection ≤ 12 weeks before initial study dosing OR currently undergoing treatment for a chronic opportunistic infection (TB, pneumocystis pneumonia, cytomegalovirus, herpes simplex virus, herpes zoster, or atypical mycobacteria)
- Acute/chronic infection requiring hospitalization ≤ 30 days before screening visit AND/OR administration of parenteral (IV or IM) antibacterial, antiviral, antifungal, or anti-parasitic agents ≤ 30 days before screening visit
- History of thrombophlebitis or thromboembolic disorders (e.g., blood clots) or serious adverse reactions to blood draws
- Medical illness (unstable cardiac disease, AIDS, liver or renal impairment, or malignant disease within 5 years before screening visit) or treatment of same that could interfere with study participation

- Neurological disorders, including but not limited to history of seizures (except childhood febrile seizures and ECT-induced seizures), dementia, history of stroke, Parkinson's disease, multiple sclerosis, cerebral aneurysm.
- History of moderate to severe traumatic brain injury (TBI); i.e., TBI that resulted in no or brief hospitalization, loss of consciousness of less than 20 minutes, post-traumatic amnesia of less than 24 hours, and no continuing side effects of the TBI (e.g., seizures, cognitive impairment, headaches)
- Frequent (more than once a week) or severe (requiring a visit to urgent care, hospital, or ED) migraines in the past 30 days before the screening visit
- DSM-V diagnosis of alcohol of substance abuse (other than nicotine) within the last month or a DSM-IV diagnosis of alcohol or substance dependence (other than nicotine) within the last 6 months
- Prior or current diagnosis of bipolar disorder, manic episodes, hypomanic episodes, or mixed episodes
- Prior or current diagnosis of a psychotic disorder
- Current use of benzodiazepines or anti-epileptic drugs
- Prior brain surgery
- Any brain devices/implants, including cochlear implants and aneurysm clips or other factors that are contraindicated for undergoing an MRI
- Non-English speakers
- Pregnancy, nursing, or if female and fertile, unwilling to use appropriate birth control measures during study participation
- Concurrent medical condition or treatment for a medical disorder that, in the opinion of the investigator, could confound interpretation of results or affect the patient's ability to fully participate in the study.
- Anything that, in the opinion of the investigator, would place the participant at increased risk or preclude the participant's full compliance with or completion of the study

5.3 LIFESTYLE CONSIDERATIONS

Benzodiazepine use will be prohibited during this study, unless used as needed. If participants are prescribed benzodiazepines as needed (PRN), they will be requested not to use benzodiazepines within 48 hours of a study session.

5.4 SCREEN FAILURES

In the design of this study, all participants will be screened by a clinician (Dr. Sheikh) who will determine eligibility based on diagnosis of SLE. However, this process does not necessarily account for all exclusion criteria.

In the case that a participant enrolls to participate in the trial, but does not meet criteria, the study coordinator completing the screening process will clearly explain why the participant does not meet criteria. However, in the case that a participant does not qualify based on suicide risk, procedures outlined below must be followed to ensure participant safety.

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

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

Dr. Lee will review sMRIs for incidental findings of malignancy prior to randomization and tACS stimulation. In cases of incidental findings, the patient will be disqualified from the study and the study team will follow Dr. Lee's recommendations regarding facilitating contact with appropriate providers for medical care. If a patient has received a clinical or research MRI in the 3 months before screening and had been found to have no evidence of malignancy, then they would not need to undergo an MRI for this study given there has been no change in clinical status or symptoms during that time.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

This clinical trial will utilize multiple recruitment strategies in order to communicate this opportunity to as many potential participants as possible, including posting ads in the local newspapers, including the Independent Weekly (free). In addition to newspapers we will have postings on websites such as ClinicalTrials.gov. We will have contact information and a brief summary of the clinical trial posted on the Carolina Center for Neurostimulation website, Thurston Arthritis Research Center Website, and on the Frohlich Lab Twitter page. These strategies will assist in recruiting patients. Finally, in addition to

these recruitment strategies, we will have information about our study with study coordinator contact information on Join the Conquest, ClinicalTrials.gov. Interested individuals need simply to read the information about the study and contact the study coordinator to complete the phone screening.

Furthermore, Dr. Saira Sheikh, principal investigator, is an expert in SLE and will be able to identify potential candidates and provide materials for those interested in enrolling among the patients seen at the UNC Rheumatology Specialty Clinic.

Our retention strategy includes a payment schedule of four times per participant. The participant will receive payment at the initial session, Days 1 through 5 of stimulation, both follow up sessions, and the final 3-month follow up. The research staff will also give each participant a reminder call for the initial session, the MRI visit, the first day of stimulation, and each follow up session. Each research staff member will be easily available for the participants to contact via email or phone. The inclusion criteria state that each participant must be able to understand all risks and benefits associated with this study. We will be asking each participant to answer questions about the consent form to determine that the study process and the duration of participation are completely understood by all participants. We will aim to have a specific research team member assigned to complete all sessions with the same participant. However we will not require the same researcher to be present during stimulation sessions 2 through 4. The study team will work hard at forming rapport with the participant so they feel comfortable and willing to discuss what may be sensitive information. Retention will be quantified by the fraction of participants coming to each scheduled session (the data from each session will be scored and documented the day of the session).

As this study requires several days of participation in a row, we will allow participants to miss one stimulation session, as long as it is made up at the end of the stimulation week. If two consecutive stimulation sessions are missed, the participant will be withdrawn from participation. This schedule would permit the participant to still receive the full intervention (5 days of stimulation) without being withdrawn from the study due to unforeseen circumstances (e.g., inclement weather, car trouble). In addition, follow-up sessions will be permitted to be scheduled ± 3 days to account for possible scheduling problems; this would permit the two-week follow-up to occur 11-17 days after completion of the intervention and the four-week follow-up to occur 25-31 days after completion of the intervention.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

We will be using the XCSITE100 stimulator designed by PulvinarNeuro 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. While the Neuroconn device is commercially available, it cannot be preprogrammed for 10Hz-tACS, cannot be monitored remotely, and is not designed for tACS clinical trials. This makes the use of the Neuroconn device not appropriate for this study.

The XSCITE100 stimulator may apply 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. tACS may be applied for currents between 100 µA and 2 mA (peak-to-peak for tACS). For the purposes of this study, this device will be set to deliver either sham stimulation, alpha-tACS, or theta-tACS.

The XCSITE100 device runs on a single 9V rechargeable battery. The device itself is run through a device on a tablet. For more instructions, please see attached instruction manual.

The stimulator has two main components:

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

6.1.2 DOSING AND ADMINISTRATION

The research team will first measure each participant's head using the 10-20 system to determine the electrode locations. Participants will then be fitted with the 3 electrodes for stimulation: two 5x5cm

electrodes placed over F3 and F4, and one 5x7cm electrode placed on Cz. Electrodes will be carbon rubber, with Ten20 conductive paste applied. During stimulation, the participant will be in a relaxed and experimentally-controlled state by watching a nature movie (such as *Reefscapes*). One session of stimulation will be performed per patient per day, for 40 minutes. Before and after the stimulation on Day 1 and Day 5 of stimulation, an eyes open resting state EEG will be performed.

Participants will be randomly assigned to one of three arms; active sham stimulation, individualized alpha-tACS (usually 8-12Hz), or individualized theta-tACS (alpha frequency minus 4 Hz). Active sham stimulation will include 20 seconds of ramp-in to 40 seconds of 10 Hz tACS with a ramp out of 20 seconds for a total of 80 seconds of stimulation. The choice of an active sham is motivated to enhance success of patient blinding by mimicking skin sensations associated with tACS. Alpha- tACS and theta-tACS will have a 20 second ramp-in and ramp-out with 40 minutes of stimulation for a total of 2440 seconds of stimulation. Stimulation waveform is a sine-wave with a zero-to-peak amplitude of 1 mA. In each arm, participants will stay in a relaxed and yet controlled state by watching a nature movie such as "Reefscape" during stimulation.

Stimulation devices will be preprogrammed and codes will be randomized to one of the two experimental arms. Researchers will enter the participant-specific code into the Asus tablet that controls the XCSITE100 device and will monitor participants during the 40 minutes of the stimulation. The study coordinator and/or the research assistant will be thoroughly trained and have trainings documented on the transcranial stimulation device and will be present during all stimulation sessions. To monitor side effects of stimulation an adverse events questionnaire will be administered after each stimulation session.

Adverse Effects Questionnaire:

Transcranial Current Stimulation Questionnaire

Did you experience any of the following? Please circle the appropriate number for each (1-4). In the last column, indicate how related the symptom is to transcranial current stimulation

1 = no relation; 2 = remote; 3 = possible; 4 = probable; 5 = definite

	Absent	Mild	Moderate	Severe	Related to Stimulation?
Headache:	1	2	3	4	
Neck pain:	1	2	3	4	
Scalp pain:	1	2	3	4	
Tingling:	1	2	3	4	
Itching:	1	2	3	4	
Ringing/Buzzing Noise:	1	2	3	4	
Burning sensation:	1	2	3	4	
Local redness:	1	2	3	4	

Sleepiness:	1	2	3	4
Trouble concentrating:	1	2	3	4
Improved mood:	1	2	3	4
Worsening of mood:	1	2	3	4
Dizziness:	1	2	3	4
Flickering lights:	1	2	3	4
Other (specify):	1	2	3	4

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.2.1 RANDOMIZATION

Angel Huang will randomize 72 6-digit codes which will be used by the study coordinator and research assistants. These codes are directly linked to which treatment participants receive (sham/placebo, individualized alpha-tACS at 1 mA, or theta-tACS at 1 mA) and will be entered into the XCSITE tablet. The assignment of each participant cannot be determined by looking at the codes (e.g., codes are not sequential, code assignment is not based on “odd” or “even” numbers). Angel Huang has no other responsibility in the study other than providing these randomized codes. In the case that Angel Huang leaves the Frohlich Lab, another equivalent researcher who does not work with human participants will perform this task.

In case of attrition, previously used codes will be used for newly randomized participants. If a participant withdraws, is withdrawn, or is lost to follow up, the codes will be reassigned.

6.2.2 BLINDING

This study is designed to be double-blind. This means that the participant and the researchers do not know of each participant's assignment until the completion of all data collection. This is accomplished by the use of the randomization codes described above.

Furthermore, this study utilizes an active sham stimulation. This means that the sham/placebo condition includes some stimulation, mimicking the skin sensations associated with tACS. In our previously concluded trial (Alexander et al., 2019), participants in the sham and 10 Hz tACS groups responded similarly to the blinding questionnaire, indicating that our active sham stimulation successfully blinded the participants.

Additionally, during the initial data analysis phase, Dr. Frohlich will be blinded to whether data and results are from sham vs active treatment in compliance with the UNC School of Medicine Conflict of Interest Committee proposed financial conflict of interest management plan.

6.3 STUDY INTERVENTION COMPLIANCE

Full compliance with the intervention is defined as completing all 5 daily stimulation sessions for 40 minutes each day. As the intervention is applied and monitored by the study coordinator(s) and research assistants, compliance can be directly observed.

6.4 CONCOMITANT THERAPY

Eligible participants will be permitted to be receiving concomitant therapy. The only medications not permitted during this trial are anticonvulsants and benzodiazepines. While the use of antidepressants, anti-inflammatories, or other therapies may improve the symptoms of SLE during the course of this study, we anticipate that this bias will be reduced by two factors: (1) prior to entry to the study, all participants will be required to be on stable SLE and psychiatric related medications (i.e., no change in administration or dose) for at least 4 weeks, and (2) the design of this study includes a control stimulation (placebo/sham). Both of these design choices will reduce the potential outside influence of concomitant therapies.

To ensure that concomitant therapies are logged appropriately, participants will be requested to report any changes to the researchers. Furthermore, concomitant therapies will be logged at the Initial Session, Day 1 of stimulation (baseline), day 5 of stimulation, and at both follow-up visits. Participants will be requested to include the dosing for these therapies (i.e., how often per day, how much in each pill, how many pills) as well as when they were first prescribed the medication.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from the week of stimulation does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The study intervention (i.e., the 5 consecutive days of stimulation) will be discontinued for the following reasons:

- A participant develops increased suicidal risk, as determined by an acute assessment by Dr. Schiller.
- A participant has a YMRS score greater than to 12.
- The participant misses two consecutive days of stimulation.
- The participant misses a single day of stimulation and is unable to make it up at the end of the stimulation week.
- Any clinical adverse event (AE), laboratory abnormality, intercurrent illness or other medical condition, or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets any exclusion criteria (either newly developed or not previously recognized).
- A participant wishes to withdraw from further participation for any reason.

If the participant withdraws from the intervention, he/she will be followed through the 4 week follow-up with the designated clinical assessments to ensure participant safety:

- HDRS
- YMRS
- Suicide Questionnaire

Additional measures may be continued if deemed appropriate (e.g., EEG, cognitive tasks, Comparative Pain Scale, Pain Catastrophizing Scale).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

A study participant will be discontinued from further participation if:

- Any clinical adverse event (AE), serious adverse event (SAE), laboratory abnormality, intercurrent illness or other medical condition, or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets any exclusion criteria (either newly developed or not previously recognized).
- A participant wishes to withdraw from further participation for any reason.

The reason for participant discontinuation or withdrawal from the study will be recorded with the participant files. Participants who sign the informed consent form and are not randomized will be replaced. Participants who sign the informed consent form, and are randomized and receive the full study intervention (5 consecutive days of 40 minutes of stimulation), and subsequently withdraw or are withdrawn or discontinue from the study will not be replaced. However, participants who sign the informed consent form, and are randomized and receive only part of the study intervention, and subsequently withdraw or are withdrawn or discontinue from the study will be replaced.

7.3 LOST TO FOLLOW-UP

All efforts will be made to ensure participants are not lost to follow-up, including developing rapport and ensuring enrolled participants are reminded of their session dates. To ensure that participants attend both follow-up sessions, study coordinators and research assistants will be flexible in timing, including offering sessions later in the day as well as some weekends.

Every effort will be made to contact participants who are lost to follow-up, including contacting via email and phone. However, if a participant is lost to follow-up, the missed sessions will be labeled as missing data and our pre-determined analysis plan takes into consideration missing data.

7.4 SUSPENSION OR TERMINATION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- 2 SAEs for up to 10 participants or 20% SAE if more than 10 (see SAE stopping rules below)
- 6 TEAEs for up to 10 participants or 40% TEAE if more than 10 (see TEAE stopping rules below)

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

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

7.4.1 SERIOUS ADVERSE EVENT (SAE) STOPPING RULES

In the event of 2 SAEs (if enrollment is less than 10 subjects), possibly or definitely associated with the study intervention, the study will be suspended and the DSMB will be notified. If enrollment is more than 10 subjects, in the event of the equivalent SAEs to 20% of study enrollment, possibly or definitely associated with the study intervention, the study will be suspended and the DSMB will be notified.

7.4.2 TREATMENT EMERGENT ADVERSE EVENT (TEAE) STOPPING RULES

The use of tACS is known to have transient, mild to moderate AEs, including phosphene perception, dizziness, skin sensation, mild headache, vertigo, pressure perception, and back pain and neck stiffness.

For the purposes of this study, a treatment-emergent adverse event (TEAE) is defined as a new event that occurs during or after first dose of study treatment that persists for 14 days or more (ie: event occurs during stimulation week and continues to persist at 2 week follow up) and is determined to be related to the study intervention.

The study will be suspended and the DSMB will be notified for TEAEs possibly or definitely related to intervention:

- in the event of 6 TEAEs (for enrollment up to 10 subjects);
- in the event of the equivalent TEAEs to 40% of study enrollment, if enrollment is more than 10 subjects

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Inclusion and exclusion criteria will be determined at the initial session, including concomitant therapies, medical history, and diagnosis, to ensure that participants are diagnosed with SLE, with low suicide risk, and free of benzodiazepines and anticonvulsant medications.

8.1.1 PHYSIOLOGICAL CHANGES

1. Resting state EEG (RSEEG) recordings will be completed at several times during the course of the study. On Day 1 and Day 5 of the intervention week, participants will complete an eyes open 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 provide a before-stimulation RSEEG on these dates to compare the baseline (Day 1) to the final day of stimulation. RSEEG will also be recorded at both follow-up visits, to determine the outlasting effects of stimulation, if any. An eyes closed RSEEG will also be collected on Day 1, Day 5, and at both follow-up visits.

2. Sustained attention task will be performed with EEG recorded. The simple reaction time task requires participants to initiate a trial by pressing a button and then when prompted push a different button. In the five-choice serial reaction time task, the task is identical except that the participant is prompted to push one of five different buttons. This task measures sustained attention during the delay period of the task between task initiation and the probe appearing.

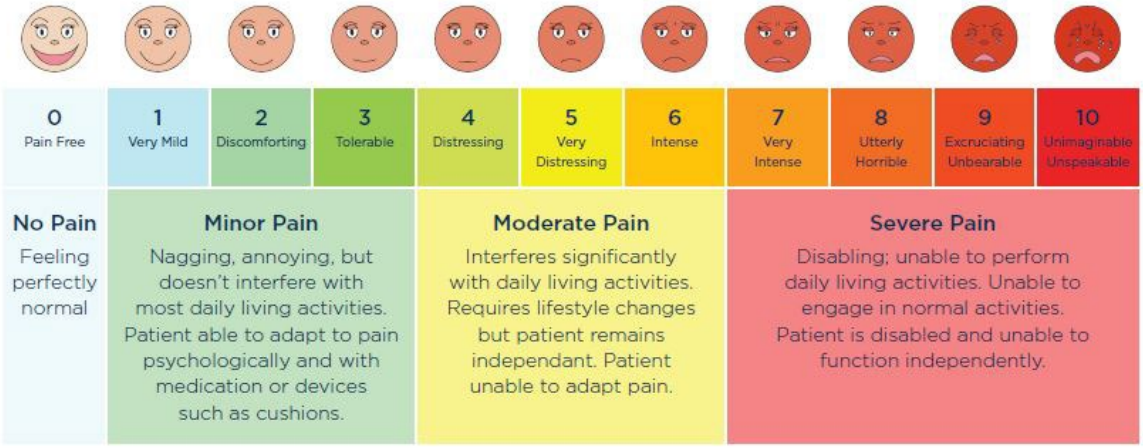
3. Selective attention task will be performed with EEG recorded. In this task, participants are instructed to orient attention to either the left or right visual field, or to both. Then, two low contrast Gabor wavelet stimuli are displayed on the screen in the left and right visual field. Each Gabor wavelet is oriented to the left or right. Finally, participants are probed as to the orientation (left or right) of the Gabor wavelet in one visual field. The attention cue to the left or right visual field is 80% predictive of which stimuli will be texted by the probe. Selective attention is the ability to improve performance with a predictive cue relative to an informative cue or an incongruent cue.

4. Working memory EEG task will be completed prior to stimulation on Day 1 and Day 5 of stimulation, as well as at both follow-up visits. In the working memory task (WM), participants must encode the color and spatial location of centrally presented squares. After a delay period with a centrally presented fixation cross, a colored square is displayed at a spatial location and participants must determine if this probe stimuli matches the encoded stimuli. By varying the number of stimuli that must be encoded, we will drive WM capacity demands that have been previous demonstrated to evoke a systematic increase in frontal theta oscillations (Jensen & Tesche, 2002) This is to assess if there are any changes in cognition from the intervention.

8.1.2 PAIN EVALUATIONS

1. The Pain Catastrophizing Scale will be assessed at baseline on Day 1 of stimulation and the 3 month follow-up. This is a questionnaire to assess self-reported pain.

2. The Comparative Pain Scale Chart will be administered at baseline, Day 1 through Day 5 of stimulation, both follow-up visits, and the 3 month follow up. This is a visual scale to assess self-reported pain.



To protect our participants during COVID-19, the assessments listed above are offered to be completed using the remote REDCap survey function (PCS and PSC).

8.1.3 CLINICAL EVALUATIONS

1. The Mini International Neuropsychiatric Interview (MINI) is a diagnostic assessment that will be administered at the initial session to determine any psychological comorbidities.

2. The Hamilton Depression Rating Scale 17-item (HDRS17) (Leentjens, Verhey, Lousberg, Spitsbergen, & Wilmink, 2000; Williams, 2001) will be administered during the initial session, day 1 of stimulation (baseline), day 5 of stimulation and at both follow-up visits. This scale is used to monitor the severity of the participant's depression symptoms, as well as determine suicide risk.

3. The Hamilton Anxiety Rating Scale (HAM-A) will be administered at baseline, day 5 of stimulation, and at both follow-up visits. This scale will be used to measure any changes in (possible) comorbid anxiety.

4. The Columbia Suicide Severity Rating Scale (C-SSRS) will be administered at the screening session, baseline, day 5 of stimulation, and at both follow-up visits. The C-SSRS is the gold-standard for assessing suicide risk and will be used, alongside self-report measures, to determine if a patient is at risk of suicide.

   To protect our participants during COVID-19, some of the assessments listed above are offered to be collected remotely over the phone or through a UNC approved video platform. These assessments include MINI , HDRS17, HAM-A, and C-SSRS.

8.1.4 PHYSICIAN ASSESSMENTS OF SLE DISEASE ACTIVITY

1. The 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria for the classification of SLE is used to diagnose lupus based on a weighted scoring system for assessments in the following areas: acute and chronic cutaneous lupus, alopecia, mucosal ulcers, arthritis, serositis, renal, neurologic, hemolytic anemia, thrombocytopenia, leukopenia or lymphopenia, as well as immunologic criteria including ANA,

low complement, Direct Coombs' test, and immunologic disorders as indicated by Anti-dsDNA, Anti-Sm, and Antiphospolipid tests. A participant is eligible if 4 of 17 criteria, including at least one clinical criterion and one immunologic criterion OR biopsy-proven lupus nephritis alone are present. The 1997 America College of Rheumatology (ACR) criteria for the classification of SLE is used to diagnose lupus based on a weighted scoring system for assessments in the following areas: malar rash, discoid rash, photosensitivity, mucosal ulcers, arthritis, serositis, renal disorders, neurologic disorders, hematologic disorders, abnormal ANA, and immunologic disorders. A participant is eligible if 4 of 11 criteria are present. These will be conducted at screening to verify patient eligibility. The patient only has to meet the threshold of the SLICC criteria OR the ACR criteria to be considered eligible for this study.

2. The Systemic Lupus International Collaborating Clinics (SLICC) SLE Damage Index assesses lupus related damage on a weighted scoring system for assessments in the following areas: ocular, neuropsychiatric, renal, pulmonary, cardiovascular, peripheral vascular, gastrointestinal, musculoskeletal, skin, gonadal, endocrine, and malignancy. Damage is defined as nonreversible change, not related to active inflammation, occurring since the onset of lupus as ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes must occur at least 6 months apart to score 2. The same lesions cannot be scored twice. This assessment will be completed by a trained investigator at screening and the 4 week follow-up.

3. The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) will be completed by a trained Investigator at screening and at the 4 week follow-up. If the 4 week follow-up visit occurs within 30 days of the screening visit, then a SLEDAI-2k will not be completed at the 4 week follow-up. This questionnaire requires a complete history, physical exam, and lab tests, to measure disease activity in SLE patients. It has 24 items covering 9 organ systems. Scores can range from 0-105 points. A score of 6 is considered clinically important and affects decision to treat.

   To protect our participants during COVID-19, some of the assessments listed above are offered to be collected remotely using UNC REDCap database and verified with the study PI during the physical exam. These assessments include the SLICC and SLICC SLE damage index.

8.1.5 SELF-REPORT ASSESSMENTS

1. The 36-Item Short Form Health Survey (SF-36) measures general health using 36 questions. There are 8 individual health "domains" or categories that each receive their own score, and from these 8 individual scores an overall score can be obtained. Overall scores can range from 0-100, with higher scores indicating better overall health.

2. The WHO Disability Assessment Schedule 2.0 (WHODAS 2.0) will be administered at baseline and the 3-month follow up to assess any comorbid disability, which could potentially affect quality of life and/or response to stimulation.

3. The Inventory of Depression and Anxiety Symptoms (IDAS) will be administered at baseline, Day 5 of stimulation, and at both follow-up visits to assess current levels of anxiety and depression.

4. The Positive and Negative Affect Schedule (PANAS) will be administered at every single study session to assess current levels of affect.

5. A blinding questionnaire will be administered on Day 5 of stimulation (Yes or No) to determine if the participant felt that they had received stimulation. Similarly, the study coordinator will also complete a blinding assessment at this point (Yes or No with a free-response space to explain why) to determine if the study coordinator believed the participant received stimulation.

To protect our participants during COVID-19, some of the assessments listed above are offered to be collected remotely using UNC REDCap database. Those assessments include: SF-36, WHODAS 2.0, IDAS, PANAS, and day 5 blinding questionnaire.

8.2 SAFETY AND OTHER ASSESSMENTS

8.2.1 SAFETY

1. A suicide questionnaire previously used in IRBs #14-0600 and #14-1622 will be used at each session of this study. This questionnaire tracks suicidal ideation and behavior. Participants will be asked to answer whether they have had any thoughts of hurting themselves within the past 24 hours (suicidal ideation, SI) and whether they have hurt themselves within the past 24 hours (suicidal behavior, SB). If a participant admits to experiencing either SI or SB their participation will be stopped immediately and their primary mental health care provider or family physician will be contacted. In the case that they do not see anyone for their depressive symptoms, Dr. Schiller will assist the participant in seeking medical care

2. The structural MRI to be used for source localization during EEG analysis will be conducted prior to randomization. The results of the T1 weighted sMRI will be reviewed by Dr. Yueh Lee for incidental findings of malignancy. If any are found, the study team will disqualify patient from study participation and will facilitate contact with providers for medical care per Dr. Lee's recommendations. Patients will complete the provided MRI screening form provided by the Biological Research Imaging Center (BRIC) prior to the sMRI screening visit.

3. A stimulation adverse effects questionnaire will be administered at the end of each stimulation session. This questionnaire will be used as a safety measure and to collect data on participant experience. This questionnaire has been used in all our previous tACS studies.

4. The Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978)was designed to assess the severity of manic symptoms at baseline, with the ability to reassess the individual's symptoms over time. When undergoing treatment that may affect depression symptoms, a possible effect of treatment is to alter the serotonin levels, potentially causing a manic episode. Although we do not expect such an event to occur since we are not using a medication that targets serotonin levels, we will be conducting this assessment at each evaluation as a precautionary measure. In the case a participant develops any sign of mania (YMRS > 12), Dr. Schiller will conduct an acute assessment to determine if the participant is experiencing mania. In the case that a participant develops mania during the week of stimulation, their participation in the study will be stopped and their primary mental health care provider or family physician will be contacted. In the case that they do not see anyone for their depression, Dr. Schiller will assist the participant in seeking medical care.

5. Urine pregnancy tests will be conducted for all female participants of reproductive age at screening and prior to stimulation on the day 1/baseline session, a negative result will be verified and documented OR a positive result will be documented and the patient will be withdrawn from the study.

To protect our participants during COVID-19, some of the assessments listed above are offered to be collected remotely over the phone or through a UNC approved video platform. These assessments include the YMRS.

8.2.2 COGNITION

1. A battery of cognitive assessments, designed to assess the cognitive deficits common in lupus, will be administered at baseline (day 1 of stimulation), day 5 of stimulation, and at both follow-up visits. This battery will be used to assess any changes in cognition following the intervention and will also be used to determine if tACS has any negative effect on cognitive abilities.

8.2.3 LABORATORY ASSESSMENTS

- **At the initial session, blood samples will be taken. These will be used to complete hematology (complete blood count, or CBC, with differential; includes white blood count, hemoglobin, hematocrit, and platelet count, which are used to score the SLEDAI 2000 assessment), as well as to assess levels of anti-dsDNA (measures levels of antibodies of double-stranded DNA, which is a diagnostic assessment of SLE) and measures of inflammation (C-reactive protein or CSR, and a complement C3/C4 panel). This same blood testing will be completed at the 4-week follow-up as well.

- **On day 1 of stimulation and at the 4-week follow-up, participants will provide a urine sample. Urinalysis, including protein/creatinine ratio and a pregnancy test (urine pregnancy lab or dipstick reading) will be assessed with this urine sample. This is for a basic assessment of overall health and is also used for the SLEDAI 2000 assessment.

**These specific assessments are imperative for completing the SLEDAI 2000. These laboratory assessments are valid for 28 days prior to the visit, so if any of these laboratories were obtained as part of routine clinical care in the preceding 28 days, they could be used to calculate the SLEDAI 2000. In clinical use, they are obtained every 3 months.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. An SAE is define as an adverse event of grade 3 or higher as determined by the U.S. Department of Health and Human Services' Common Terminology Criteria for Adverse Events (CTCAE Version 5.0 Published: November 27th, 2017).

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

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

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

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

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other

drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

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

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

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

8.3.3.3 EXPECTEDNESS

The principal investigators (Dr. Saira Sheikh, expert in SLE and Dr. Flavio Frohlich, expert in non-invasive brain stimulation) will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

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

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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

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

The study coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the 3-month follow up (end of study participation). At each study visit, the study coordinator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

We will be adopting the following table for reporting procedures:

What Event is Reported	When is Event Reported	By Whom is Event Reported	To Whom is Event Reported
Fatal or life-threatening unexpected, suspected serious adverse reactions	Within **24 hours** of initial receipt of information	Investigator	• Local/internal IRBs, DSMB
Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions	Within **48 hours** of initial receipt of information	Study Coordinator	• Local/internal IRBs/Institutional Officials, DSMB
Unanticipated adverse device effects	Within **7** working days of investigator first learning of effect	Investigator	• Local/internal IRBs
Unanticipated Problem that is not an SAE	Within **7 days** of the investigator becoming aware of the problem	Investigator	• Local/internal IRBs/Institutional Officials,

8.3.6 REPORTING OF PREGNANCY

Pregnancy tests will be administered at the initial screening session as well as before treatment on the first stimulation visit to all women of child-bearing potential. There are no studies that suggest tACS would interfere with pregnancy. However, should a participant become pregnant during the study their participation will be immediately terminated and will be sent to consult with Co-I.

Following withdrawal, the patient will be followed through the 4 week follow-up with the designated clinical assessments to ensure participant safety: HDRS, YMRS, Suicide Questionnaire. Additional measures may be continued if deemed appropriate (e.g., EEG, cognitive tasks, Comparative Pain Scale, Pain Catastrophizing Scale)

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

If an UE occurs, the IRB will be notified and the study will be adjusted as needed to protect the health and safety of the participants. Depending on the nature of the UE, the research protocol, inclusion/exclusion criteria, and informed consent will be changed to reflect the possibility of this event reoccurring. During this time, no new participants will be recruited and the research procedures for currently enrolled participants will be stopped. Each UE will be recorded and reported throughout the study.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Any new information gained during the study that may affect a participant's willingness to continue participating will be reported to all currently enrolled participants.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

9.1.1 PRIMARY EFFICACY HYPOTHESIS

Null hypothesis: There is no difference in changes of alpha frequency power between baseline (Day 1) RSEEG and RSEEG at completion of stimulation (Day 5) between treatment regimens.

Alternate hypothesis: There is a difference in changes of alpha frequency power between baseline (Day 1) RSEEG and RSEEG at completion of stimulation (Day 5) between treatment regimens.

9.1.2 SECONDARY EFFICACY HYPOTHESIS

Null hypothesis: There is no relationship between the changes in alpha frequency power and the changes in depression (using the IDAS and HDRS), pain (using the comparative pain scale and pain catastrophizing scale), and cognition (using the sustained attention task, selective attention task, working memory task, and FSMC).

Alternate hypothesis: There is a relationship between the changes in alpha frequency power and the changes in depression (using the IDAS and HDRS), pain (using the comparative pain scale and pain catastrophizing scale), or cognition (using the sustained attention task, selective attention task, and working memory task, and FSMC).

9.2 SAMPLE SIZE RATIONALE

At this point in time, no clinical trial has been completed using tACS to treat SLE. However, the Carolina Center for Neurostimulation has run several trials similar to this, including a clinical trial assessing the use of tACS to treat depression over the course of a 5-day, 40-minute stimulation paradigm (Alexander et al., 2019).

This study is a critically necessary preliminary step in this line of research. The most important aspects of the study are its exploratory analyses, its provision of point- and interval-estimates of parameters of interest, and the logistical feasibility and tolerability information it will provide. The levels of precision of the estimators of interest are important; e.g., based on a previous tACS intervention study (Alexander et al., 2019)with a mean alpha oscillatory difference of ~2 and SD≈1.2 and alpha set at .05, we anticipate N=20 per group will provide more than 80% power. The effect size was based off the difference between active tACS and sham stimulation. This study will also provide an initial indication of whether it is plausible that tACS may have beneficial effects for the target lupus population. Based on the anticipated

precision of estimators, power levels of test procedures, availability of research subjects, and stage of this line of research, we believe the study is likely to achieve its specific aims; i.e., there is low risk the study will be uninformative/inconclusive.

9.3 POPULATIONS FOR ANALYSES

Every effort will be made to ensure all enrolled and randomized participants complete all study sessions as described in this protocol. However, a priori, we determine that our population for analysis will be a per-protocol analysis dataset, indicating that only those who complete the intervention (i.e., the 5 days of stimulation) will be included in the analysis. For this study, enrolled eligible participants will be randomized to receive 5 consecutive days of stimulation. If a participant completes the intervention (i.e., receives all 5 consecutive days of stimulation), they will be included in all analyses moving forward.

Reasons for missing data (e.g., missing follow-up sessions) and reasons for participant withdrawal will be documented within the master list.

As stated previously in *Section 7 Study Intervention Discontinuation and Participant Discontinuation/Withdrawal*, enrolled participants who do not complete the full intervention will not be included in this analysis. Therefore, with this population for analysis plan, we anticipate having data from at least 45 participants that are eligible for analysis.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

All testing described below assumes a significance threshold of $p = 0.05$. All hypothesis tests that are observed to not be statistically significant will be reported as being inconclusive. Continuous data will be described using means and standard deviations, while categorical data will be described using counts/percentages. All statistical estimates of population parameters will be tabulated along with their corresponding confidence intervals (CIs).

Sensitivity analyses will be used to evaluate the robustness of the main results to reasonable perturbations of the statistical models and assumptions used.

Dr. Flavio Frohlich will be responsible for statistical computations for data analyses. During the initial data analysis phase, Dr. Frohlich will be blinded to whether data and results are from sham vs active treatment in compliance with the UNC School of Medicine Conflict of Interest Committee proposed financial conflict of interest management plan.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY OUTCOME MEASURE(S)

We will perform spectral analysis of resting state EEG from day 1 of stimulation (baseline) to day 5 of stimulation. We will use a general linear mixed-effects model (GLMM) to assess if there is statistically significant interaction between treatment (sham/placebo, theta-tACS and alpha-tACS) and session (baseline/Day 1 of stimulation, day 5 of stimulation, 2-week follow-up, 4-week follow-up). Spectral analysis will be performed with multitapered estimation of the frequency spectrum followed by integration over the classical alpha EEG band (usually 8-12 Hz). In a separate analysis, we will perform spectral analysis of resting state EEG before and after each separate stimulation session. These analyses will be completed on the per-protocol dataset.

In our previous study, which used a 5-day protocol in patients with depression (Alexander et al., 2019), we found that a correlation between the log-transformed baseline alpha power (dB) and the alpha power changes at the end of the intervention (Day 5) in all regions. We chose to use the log-transformed baseline alpha power as a covariate. We will use this same covariate in these analyses as well.

Results from this section will be described in mean decibel (dB) change and presented using spectral images for visualization.

9.4.3 ANALYSIS OF THE SECONDARY OUTCOME MEASURE(S)

Using the EEG results described in 9.4.2, mean dB change from baseline will be correlated with normalized change in HDRS* as well as the other described measures. Correlations will be assessed using Pearson's r and data will be plotted against the best fit line to visualize the results.

*HDRS normalization:

$$\frac{\text{[HDRS score at Visit \#] - [HDRS score at baseline]}}{\text{[HDRS score at baseline]}}$$

9.4.4 SAFETY ANALYSES

Safety will be assessed with a suicide questionnaire, the Columbia-Suicide Severity Rating Scale (C-SSRS), an adverse effects questionnaire, and the Young Mania Rating Scale (YMRS).

The suicide questionnaire is used as a screening to assess increase in suicidal ideation (SI) or suicidal behavior (SB). If a participant's responses indicate SI or SB, the participant will be contacted and an acute assessment will be completed if necessary by Dr. Schiller. Any verified increases in suicidal ideation will be described in counts/percentages and compared between groups using chi-square tests.

The adverse effects questionnaire will be administered following every stimulation session, for a total of 5 administrations per participant. The adverse effects questionnaire inquires about 14 possible adverse effects associated with electrical stimulation, rated on a scale of 1 (absent) to 4 (severe). Paired t-tests

with random effect "participant" will be calculated per adverse effect to determine if there are any differences in adverse effect severity between groups (sham/placebo, alpha-tACS, theta-tACS). Severity per adverse effect will be described with mean and standard deviation.

The Young Mania Rating Scale (YMRS) will be used to assess any development of mania over the course of treatment. A YMRS score of greater than 12 indicates the possible development of a manic episode. Any participant who scores greater than 12 on the YMRS will be assessed by Dr. Schiller. Any verified manic episode will be described in counts/percentages and compared between groups using a chi-square test.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

All baseline descriptive statistics will be described in terms of counts (where applicable) and means/standard deviations (where applicable).

9.4.6 PLANNED INTERIM ANALYSES

Blinded interim descriptive analyses on the safety measures (blinded adverse effects, responses to the suicide assessment, cognitive scores from the cognitive battery, as well as any adverse events) will be provided to the Data Safety and Monitoring Board (DSMB) every 6 months.

Additionally, in the event of 2 SAEs (if enrollment is less than 10 subjects), possibly or definitely associated with the study intervention, the study will be suspended and the DSMB will be notified. If enrollment is more than 10 subjects, in the event of the equivalent SAEs to 20% of study enrollment, possibly or definitely associated with the study intervention, the study will be suspended and the DSMB will be notified.

If there is reason to view unblinded information, the DSMB will directly receive the list of participants' identification numbers from Angel Huang. Participant identification number will be displayed in a table according to the three arms of the study; however, the specific treatment of each arm will not be disclosed. This will allow the DSMB to compare the three intervention groups.

There are no other planned interim analyses.

9.4.7 SUB-GROUP ANALYSES

Sub-group analyses will not be used in this study, as the sample size is too small to conduct analyses based on age, sex, race/ethnicity or other demographic characteristic(s).

9.4.8 EXPLORATORY ANALYSES

We have previously described two exploratory outcomes:

1. To investigate the outlasting effects, if any, of tACS on brain activity and clinical measures.

2. To investigate whether tACS increases cognitive control signals during cognitive tasks that probe sustained attention, selective attention, and working memory.

For (1), we will follow the same analyses as described in 9.4.2 through the two follow-up visits. For (2), we will calculate correlations between frontal midline alpha and theta activity (as measured from EEG recordings) and accuracy at cognitive tasks (reaction time for attention tasks, accuracy for working memory task). The resulting data may be used as covariates (if deemed appropriate) or may just be used as preliminary data for future studies.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of tACS will be provided to the participants and their families. Consent forms describing, in detail, the study intervention, device, procedures, and risks are given to the participant and written documentation of informed consent is required prior to the administration of any treatment or assessments used in this study. All consent forms will be IRB-approved and updated with any new information as modifications are made throughout the study.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Together, the researcher and potential participants will review the clinical trial in its entirety. At several intervals during the consent review, the researcher will ask the participant questions that will assess the comprehension of the information in the consent. If the participant is unsure or does not know, the researcher will return to that section and more carefully explain the information. Participants must sign the informed consent document prior to any procedures taking place. If needed, the participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

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

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

- Determination of unexpected, significant, or unacceptable risk to participants

- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

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

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the research team. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants.

All data will only be referenced by dummy identifier code. Data will be stored on a password protected computer. A key connecting names and code numbers will be kept in a locked cabinet, accessible only by research personnel. All data will be stored and analyzed on password protected computers, also only accessible by research personnel. Participants will not be identified in any report or publication about this study and there is no risk of deductive disclosure.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored within the Carolina Center for Neurostimulation/Frohlich Lab. After the study is completed, the data will be fully de-identified and archived within a locked file cabinet within the Thurston Arthritis Research Center.

Electronic files will be stored on secure UNC servers using either restricted access departmental drives or the REDCap database for this study.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Saira Sheikh, MD** The University of North Carolina at Chapel Hill - Department of Rheumatology szsheikh@email.unc.edu (984) 974-4191
Co-Principal Investigator	**Flavio Frohlich, PhD** The University of North Carolina at Chapel Hill - Department of Psychiatry flavio_frohlich@med.unc.edu (919) 966-4584
Co-Investigator	**Crystal Schiller, PhD** The University of North Carolina at Chapel Hill - Department of Psychiatry crystal_schiller@med.unc.edu (919) 966-4810
Co-Investigator	**Yueh Lee, MD, PhD**

The University of North Carolina at Chapel Hill –
Department of Radiology
yueh_lee@med.unc.edu
(919) 537-3730

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a DSMB under the direction of the NC TraCS Institute. Members of the DSMB will be independent from the study conduct and free of conflict of interest. The DSMB will review AEs every 6 months whereas the PI and/or Co-I will review AEs in real time and make decisions as of participant's continuation of the clinical trial. The PI will review AEs as appropriate with research team and may request additional review by Co-I on a case-by-case basis.

10.1.7 CLINICAL MONITORING

The Purpose of the monitoring plan is to present the Carolina Center for Neurostimulaton's approach to monitoring clinical trials. The plan facilitates compliance with good clinical practice.

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

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

10.1.7.1 THE CAROLINA CENTER FOR NEUROSTIMULATION MONITORING PLAN

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

Data will be verified for completeness following every study session and all data will be entered into REDCap, a secure online database. After a participant has completed his/her participation (full completion through the 3-month follow-up visit or because he/she withdrew prior to completion), data will be re-reviewed for completeness and accuracy. After all data have been collected, data will be re-reviewed by another study coordinator or research assistant who was not involved with the data collection process.

AE and SAE are clearly defined in the Master Protocol. Documents of AE and SAE can be found in the study binder on file within Medical School Wing C, Room 233. It is responsibility of the study coordinator to report all events to the PI. Reporting of AEs and SAEs is described within *Section 8.3.*

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

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

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

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

The study coordinator and research assistants will be responsible for the informed consent process, review for eligibility, questionnaire administration, data entry, device administration, EEG administration, and CRF entries. The study coordinator will be responsible for AE/SAE documentation and reporting, while the PI will be responsible for the AE assessment, review of the AE documentation forms and overview of the research staff.

REDCap will serve as a secure data management tool for this study. Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a data capture system provided by REDCap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. The study coordinator and research assistants will have complete access to the REDCap system, while the PIs and Co-I will have read only ability. This will enable the researchers to enter the data and the PIs and Co-I to review.

10.1.9.2 STUDY RECORDS RETENTION

According to the University of North Carolina at Chapel Hill's Archives and Record Management Services schedule for General Records Retention and Disposition Schedule 6.10, records will be kept for 5 years after the completion of the study.

10.1.10 PROTOCOL DEVIATIONS

All deviations from the protocol will be addressed in study participant source documents. The researcher will complete a Protocol Deviation Log using the participant code as the identifier. This form will collect information such as the date the deviation occurred, details of what the deviation consisted of, any corrective and preventative actions that were taken as a result of the deviation, and the date that the PI and IRB were notified. The PI will review the information and initial once approved. A completed copy of the Protocol Deviation Form will be maintained in the regulatory file, as well as in the participant's source document. Protocol deviations will be sent to the IRB per their guidelines. The site PI/study staff will be responsible for knowing and adhering to their IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be registered on ClinicalTrials.gov once IRB approved. The aim is to publish the results of this study in a peer-reviewed, highly-ranked journal.

The raw data will be preserved and available upon request after any publication submission or public presentation.

10.1.12 CONFLICT OF INTEREST POLICY

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

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS

AE	Adverse Event
ACR	American College of Rheumatology
ANA	Antinuclear antibody test
ANOVA	Analysis of Variance
Anti-dsDNA	Anti-double stranded DNA

CBC	Complete blood count
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COC	Certificate of Confidentiality
CRP	C-reactive protein
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual, 5th Edition
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
EEG	Electroencephalogram
ENA	Extractable Nuclear Antigen Antibodies
FSMC	Fatigue Scale for Motor and Cognitive Functions
GCP	Good Clinical Practice
HAM-A	Hamilton Anxiety Rating Scale
HDRS	Hamilton Depression Rating Scale
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IDAS	Inventory of Depression and Anxiety Symptoms
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
MINI	Mini International Neuropsychiatric Interview
MRI	Magnetic Resonance Imaging
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PCR	Polymerase Chain Reaction
PCS	Pain Catastrophizing Scale
PI	Principal Investigator
PNAS	Positive and Negative Affect Schedule
QA	Quality Assurance
QC	Quality Control
RSEEG	Resting state EEG
SAE	Serious Adverse Event
SF-36	36-Item Short Form Health Survey
SLE	Systemic Lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics

sMRI	Structural Magnetic Resonance Imaging
SOA	Schedule of Activities
SOP	Standard Operating Procedure
tACS	Transcranial alternating current stimulation
TEAE	Treatment Emergent Adverse Event
UP	Unanticipated Problem
US	United States
WHODAS	WHO Disability Assessment Schedule
YMRS	Young Mania Rating Scale

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.1	5/30/19	Addition of Dr. Yueh Lee as Co-investigator	Dr. Lee, a neuroradiologist, will review MRI scans and handle incidental findings as needed.
1.2	7/25/19	Clarifying sMRI timing and safety review process Updating urine pregnancy test timing per UNC IRB stipulation Updating data blinding procedures and data sharing policy per UNC SOM COI Committee FCOI management plan for Dr. Frohlich Adjusted CANTAB to be computerized for EEG recording	Bringing protocol in compliance with UNC IRB stipulations and COI Committee management plan Editing for clarity and typos Leverages additional scientific value from the dataset
1.3	9/4/19	Updating personnel responsibilities Updating urine pregnancy test timing Updating study layout Adding cheek swab for *bartonella* testing Remove NAMI from recruitment Remove pressure pain threshold Adding Pain Catastrophizing Scale Replacing FSS with FSMC Replacing STAI with IDAS Removed SLAQ, PROMIS, and ESR	Charles Zhou has left the lab, his responsibilities have been given to Angel Huang. FSMC is a more comprehensive measure for self-reporting of cognitive fog. The IDAS is a better measure to assess the change in depression and anxiety symptoms over time. These assessments were not necessary for evaluating objectives.

1.4	11/14/19	clarifying inclusion criteria and discontinuation criteria for YRMS, a score of greater than (>) 12 is considered a manic episode and is sufficient for screen-failure or discontinuation. clarifying secondary objective, the SF-36 will be evaluated at screening and 4 week follow-up, all other measures will be evaluated at baseline to Day 5 as previously approved.	Clarifying protocol
1.5	11/25/19	Removing blood draws to test for *Bartonella*	We have removed Bartonella as an exploratory outcome – thus, the data is not needed
1.6	01/24/2020	Correcting HDRS17 language in study assessments and procedures to match eligibility criteria.	Providing clarification for discrepancies
1.7	2/28/2022	Clarification of sMRI imaging Updated and specified study suspension/termination rules for probably or definitely related AEs Added DSMB to adverse event reporting for Fatal or life threatening unexpected, suspected serious adverse reactions Added optional remote completion for consent through REDCap, patient self-report questionnaires, and clinical psychological assessments through the REDCap database and phone/UNC approved video platform	Clarification Per DSMB request description and Per DSMB request Protection of high-risk patients during COVID-19 and to be continue throughout the remainder of the study

11 REFERENCES

Ahn, S., Prim, J. H., Alexander, M. L., McCulloch, K. L., & Frohlich, F. (2019). Identifying and Engaging Neuronal Oscillations by Transcranial Alternating Current Stimulation in Patients With Chronic Low Back Pain: A Randomized, Crossover, Double-Blind, Sham-Controlled Pilot Study. *J Pain, 20*(3), 277 e271-277 e211. doi:10.1016/j.jpain.2018.09.004

Alexander, M. L., Alagapan, S., Lugo, C. E., Mellin, J. M., Lustenberger, C., Rubinow, D. R., & Frohlich, F. (2019). Double-blind, randomized pilot clinical trial targeting alpha oscillations with transcranial alternating current stimulation (tACS) for the treatment of major depressive disorder (MDD). *Transl Psychiatry, 9*(1), 106. doi:10.1038/s41398-019-0439-0

Arendsen, L. J., Hugh-Jones, S., & Lloyd, D. M. (2018). Transcranial Alternating Current Stimulation at Alpha Frequency Reduces Pain When the Intensity of Pain is Uncertain. *J Pain, 19*(7), 807-818. doi:10.1016/j.jpain.2018.02.014

Azizoddin, D. R., Gandhi, N., Weinberg, S., Sengupta, M., Nicassio, P. M., & Jolly, M. (2018). Fatigue in systemic lupus: the role of disease activity and its correlates. *Lupus*, 961203318817826. doi:10.1177/0961203318817826

Dall'Era, M., Bruce, I. N., Gordon, C., Manzi, S., McCaffrey, J., & Lipsky, P. E. (2019). Current challenges in the development of new treatments for lupus. *Annals of the Rheumatic Diseases*, annrheumdis-2018-214530. doi:10.1136/annrheumdis-2018-214530

de Amorim, J. C., Frittoli, R. B., Pereira, D., Postal, M., Dertkigil, S. S. J., Reis, F., . . . Appenzeller, S. (2019). Epidemiology, characterization and diagnosis of neuropsychiatric events in systemic lupus erythematosus. *Expert Rev Clin Immunol*. doi:10.1080/1744666X.2019.1564040

Frohlich, F., & McCormick, D. A. (2010). Endogenous electric fields may guide neocortical network activity. *Neuron, 67*(1), 129-143. doi:10.1016/j.neuron.2010.06.005

Gotlib, I. H., & Joormann, J. (2010). Cognition and depression: current status and future directions. *Annu Rev Clin Psychol, 6*, 285-312. doi:10.1146/annurev.clinpsy.121208.131305

Herrmann, C., Rach, S., Neuling, T., & Strüber, D. (2013). Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. *Frontiers in Human Neuroscience, 7*(279). doi:10.3389/fnhum.2013.00279

Jensen, O., & Tesche, C. D. (2002). Frontal theta activity in humans increases with memory load in a working memory task. *European Journal of Neuroscience, 15*(8), 1395-1399. doi:doi:10.1046/j.1460-9568.2002.01975.x

Khan, A., Khan, S. R., Shankles, E. B., & Polissar, N. L. (2002). Relative sensitivity of the Montgomery-Asberg Depression Rating Scale, the Hamilton Depression rating scale and the Clinical Global Impressions rating scale in antidepressant clinical trials. *Int Clin Psychopharmacol, 17*(6), 281-285.

Leentjens, A. F., Verhey, F. R., Lousberg, R., Spitsbergen, H., & Wilmink, F. W. (2000). The validity of the Hamilton and Montgomery-Asberg depression rating scales as screening and diagnostic tools for depression in Parkinson's disease. *International journal of geriatric psychiatry, 15*(7), 644-649.

Mackay, M. (2015). Lupus brain fog: a biologic perspective on cognitive impairment, depression, and fatigue in systemic lupus erythematosus. *Immunologic research, 63*(1-3), 26-37. doi:10.1007/s12026-015-8716-3

Pinheiro, E. S., de Queiros, F. C., Montoya, P., Santos, C. L., do Nascimento, M. A., Ito, C. H., . . . Baptista, A. F. (2016). Electroencephalographic Patterns in Chronic Pain: A Systematic Review of the Literature. *PLoS One, 11*(2), e0149085. doi:10.1371/journal.pone.0149085

Ploner, M., Sorg, C., & Gross, J. (2017). Brain Rhythms of Pain. *Trends in cognitive sciences, 21*(2), 100-110. doi:10.1016/j.tics.2016.12.001

Stitt, I., Zhou, Z. C., Radtke-Schuller, S., & Frohlich, F. (2018). Arousal dependent modulation of thalamo-cortical functional interaction. *Nat Commun, 9*(1), 2455. doi:10.1038/s41467-018-04785-6

Tunks, E. R., Crook, J., & Weir, R. (2008). Epidemiology of chronic pain with psychological comorbidity: prevalence, risk, course, and prognosis. *Can J Psychiatry, 53*(4), 224-234. doi:10.1177/070674370805300403

Williams, J. B. W. (2001). Standardizing the Hamilton Depression Rating Scale: past, present, and future. *European Archives of Psychiatry and Clinical Neuroscience, 251*(2), 6-12. doi:10.1007/bf03035120

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: Reliability, validity and sensitivity. *The British Journal of Psychiatry, 133*, 429-435. doi:10.1192/bjp.133.5.429