

**EFFECT OF TRANSCRANIAL ALTERNATING CURRENT STIMULATION IN
CHRONIC LOW BACK PAIN: A PILOT STUDY**

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CONFIDENTIAL

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Effect of Transcranial Alternating Current Stimulation in Chronic Low Back Pain: A Pilot Study

A PILOT, RANDOMIZED, CROSSOVER, DOUBLE-BLIND, SHAM-CONTROLLED, SINGLE-SITE STUDY OF THE
EFFECT OF TRANSCRANIAL ALTERNATING CURRENT STIMULATION IN SUBJECTS WITH CHRONIC LOW
BACK PAIN

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS 6

STUDY SUMMARY..... 9

1 KEY ROLES..... 10

1.1 INDIVIDUALS..... 10

1.2 INSTITUTIONS 11

1.3 OPTIONAL..... 11

1.4 FUNDING SOURCES 11

2 INTRODUCTION..... 12

2.1 BACKGROUND 12

2.2 INVESTIGATIONAL AGENT..... 13

2.3 DOSE RATIONALE 13

2.4 STUDY AIMS/HYPOTHESES..... 13

2.4.1 PRIMARY OBJECTIVE 14

2.4.1 SECONDARY OBJECTIVE 14

3 SUBJECT SELECTION AND WITHDRAWAL 15

3.1 INCLUSION CRITERIA 15

3.2 EXCLUSION CRITERIA..... 15

3.3 STRATEGIES FOR RECRUITMENT AND RETENTION 16

3.3.1 RECRUITMENT 16

3.3.2 RETENTION 16

4 BASIC STUDY DESIGN 18

4.1 TREATMENT ASSIGNMENT PROCEDURES 18

4.1.1 RANDOMIZATION PROCEDURES..... 18

5 STUDY SCHEDULE..... 20

5.1 SCREENING..... 20

5.1.1 SCREENING TELEPHONE CALL..... 20

5.1.2 INITIAL SCREENING SESSION (VISIT 1) 20

5.2 STIMULATION SESSIONS..... 21

5.2.1 DAY 1 OF STIMULATION (VISIT 1 CONTINUED) 21

5.2.2 DAYS 2 OF STIMULATION (VISIT 2)..... 21

5.3 FOLLOW-UP..... 21

5.3.1	FOLLOW-UP EMAIL	21
5.3.2	UNBLINDING PROCEDURES.....	21
6	<u>STUDY PROCEDURES/EVALUATIONS.....</u>	22
6.1	SELF-REPORT MEASURES	22
6.2	CLINICAL MEASURES	22
6.3	SPECIAL ASSAYS OR PROCEDURES.....	22
6.3.1	SPECIAL PROCEDURES.....	22
6.3.2	EKG PROCEDURES	23
6.3.3	PRESSURE PAIN THRESHOLD	23
	EEG PROCEDURES	23
6.4	SAFETY MEASURES	23
6.5	LABORATORY EVALUATIONS.....	23
6.5.1	SCREENING LABORATORY EVALUATIONS	23
6.5.2	SALIVA SAMPLE	24
7	<u>STUDY INVESTIGATIONAL PRODUCT.....</u>	25
7.1	SAFETY FEATURES.....	25
7.2	PREPARATION AND ADMINISTRATION OF STUDY INVESTIGATIONAL PRODUCT	26
7.3	ASSESSMENT OF PARTICIPANT COMPLIANCE WITH STUDY INVESTIGATIONAL PRODUCT	27
8	<u>POTENTIAL RISKS AND BENEFITS.....</u>	28
8.1	BENEFITS TO SUBJECTS AND SOCIETY	28
8.2	POTENTIAL RISKS.....	28
8.2.1	PSYCHOLOGICAL	28
8.2.2	PHYSICAL	29
8.3	REFERRALS FOR MEDICAL FOLLOW-UP OR PSYCHOLOGICAL COUNSELING	29
8.3.1	PREGNANCY FOLLOW-UP.....	29
9	<u>DATA AND SAFETY MONITORING</u>	31
9.1	FROHLICH LAB MONITORING PLAN	31
9.3	EARLY WITHDRAWAL OF PARTICIPANTS	32
9.3.1	REASONS FOR WITHDRAWAL.....	32
9.3.2	DATA COLLECTION AND FOLLOW-UP FOR WITHDRAWN PARTICIPANTS	32
9.4	TERMINATION OF STUDY.....	32
10	<u>SAFETY & REPORTING</u>	33
10.1	SAFETY PARAMETERS	33
10.2	METHODS AND TIMING FOR ASSESSING, RECORDING, AND ANALYZING SAFETY PARAMETERS	33
10.2.1	ADVERSE EVENTS	33
10.2.1	SERIOUS ADVERSE EVENTS	34

10.2.2 UNANTICIPATED PROBLEMS..... 35

10.3 REPORTING PROCEDURES..... 35

10.3.1 REPORTING OF PREGNANCY..... 36

10.4 TYPES AND DURATION OF FOLLOW-UP OF PARTICIPANTS AFTER ADVERSE EVENTS 36

11 STATISTICAL PLAN..... 37

11.1 STATISTICAL ANALYSIS STRATEGIES 37

11.2 SAMPLE SIZE DETERMINATION..... 37

11.3 DATA MANAGEMENT 37

12 DATA HANDLING AND RECORD KEEPING..... 38

12.1 PHI AND HIPAA 38

12.2 CONFIDENTIALITY 38

12.2.1 ACCESS TO SOURCE DOCUMENTS 38

12.2.2 SENSITIVE INFORMATION 38

12.2.3 OTHER..... 39

12.3 SOURCE DOCUMENTS..... 39

12.4 DATA MANAGEMENT RESPONSIBILITIES 40

12.5 DATA CAPTURE METHODS (REDCAP) 40

12.6 PROTOCOL DEVIATIONS..... 40

12.7 RECORD RETENTION..... 40

13 ETHICAL CONSIDERATIONS 41

13.1 ETHICAL STANDARD 41

13.2 INSTITUTIONAL REVIEW BOARD (IRB) 41

13.3 INFORMED CONSENT PROCESS 41

13.4 EXCLUSION OF WOMEN, MINORITIES, AND CHILDREN (SPECIAL POPULATIONS)..... 42

13.5 PARTICIPANT CONFIDENTIALITY 42

13.6 STUDY DISCONTINUATION..... 42

14 PUBLICATION POLICY..... 43

15 LITERATURE REFERENCES..... 44

ZAEHLE, T., RACH, S., & HERRMANN, C. S. (2010). TRANSCRANIAL ALTERNATING CURRENT STIMULATION ENHANCES INDIVIDUAL ALPHA ACTIVITY IN HUMAN EEG. PLOS ONE, 5(11), E13766.... 47

APPENDIX A: SCHEDULE OF EVENTS 48

APPENDIX B: AE REPORT FORM..... 49

APPENDIX C: IRB AMENDMENT TRACKING LOG 51

APPENDIX D: AE REPORT FORM..... 52

APPENDIX E: INFORMED CONSENT QUIZ 53

APPENDIX F: NOTE TO FILE 54

APPENDIX G: TELEPHONE SCRIPT..... 55

LIST OF ABBREVIATIONS

5x SST	Five Times Sit-to-Stand Test
AE	Adverse Event/Adverse Experience
ANOVA	Analysis of Variance
BIS/BAS	Behavioral Inhibition System / Behavioral Approach System
CFR	Code of Federal Regulations
cLBP	Chronic low back pain
CNS	Central Nervous System
Co-I	Co-Investigator
CRF	Case Report Form
DASS-21	Depression Anxiety Stress Scale
DSMB	Data and Safety Monitoring Board
DVPRS	Defense and Veterans Pain Rating Scale
eCRF	Electronic Case Report Form
EEG	Electroencephalogram
EKG	electrocardiogram
ERP	Event Related Potential
FDA	Food and Drug Administration
FTF	Fingertip-to-Floor Test
GCP	Good Clinical Practice
HAM-D	Hamilton Psychiatric Rating Scale for Depression
HIPAA	Health Insurance Portability and Accountability Act
HRV	Heart Rate Variability
Hz	Hertz
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IRI	Interpersonal Reactivity Index
JAMA	Journal of the American Medical Association
LAR	Legally Authorized Representative
LBP	Low back pain
MCIS	minimally clinical important difference
NAMI	National Alliance on Mental Illness
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NRB	Neurosciences Research Building
ODI	Oswestry Disability Index
OHRE	Office of Human Research Ethics
OHRP	Office for Human Research Protections
PCS	Pain catastrophizing Scale
PFC	Pre-frontal cortex

PHI	Protected Health Information
PI	Principal Investigator
PSEQ	Pain Self-Efficacy Questionnaire
rTMS	repetitive transcranial magnetic stimulation
SAE	Serious Adverse Event/Serious Adverse Experience
SB	Suicidal Behavior
SI	Suicidal Ideation
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SPI	Serial Peripheral Interface
tACS	Transcranial Alternating Current Stimulation
tACS	Transcranial Alternating Current Stimulation
tDCS	transcranial direct current stimulation
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
UE	Unexpected Event
UNC	University of North Carolina
UNC-CH	University of North Carolina at Chapel Hill
US	United States
VAS	Visual Analog Scale

STUDY SUMMARY	
Title	<i>EFFECT OF TRANSCRANIAL ALTERNATING CURRENT STIMULATION IN CHRONIC LOW BACK PAIN: A PILOT STUDY</i>
Short Title	CPS
Protocol Number	17-0870
Phase	<i>Pilot</i>
Methodology	<i>Double-blind, randomized, active sham controlled, cross-over, single site</i>
Study Duration	<i>This study is expected to last 6 months</i>
Study Center(s)	<i>This is a single-site study performed at The University of North Carolina at Chapel Hill.</i>
Objectives (Purpose)	<i>To test the feasibility of using tACS to treat patients with chronic pain, and to collect pilot efficacy and EKG biomarker data for optimizing the design of subsequent large-scale studies. The treatment rationale is to renormalize the presumed pathological structure of alpha oscillations in the prefrontal cortex (PFC) of patients with chronic pain.</i>
Number of Subjects	20
Diagnosis and Main Inclusion Criteria	<i>Eligible participants will be patients who have a diagnosis of chronic pain as defined by a clinician, a >4 on a VAS self-report pain rating, not taking opioids, and have low suicide risk.</i>
Description of Intervention (Procedures/methods)	<i>20 participants will be randomized into one of two arms: to receive either 40 minutes of sham tACS or 40 minutes of 10 Hz tACS during their first stimulation visit (then crossover the next visit) while in a relaxed, yet experimentally controlled state, by watching a nature movie such as "Reefscape" during stimulation.</i>
Related IRB Applications	n/a

1 KEY ROLES

1.1 INDIVIDUALS

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1.4 FUNDING SOURCES

Please list below the funding sources for this project:

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National Institute of Mental Health (NIMH)	R01MH101547	Federal			

External Funding: This project is externally funded but UNC-CH is not the direct recipient of federal funds.

UNC-CH Funding: This project is not funded through UNC-CH.

Classified: This project is not classified.

2 INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to U.S. and international standards of Good Clinical Practice (FDA Title 21 Part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

2.1 BACKGROUND

Chronic pain is a severe disabling problem within society, affecting 25-30% of the United States population (Baliki and Apkarian, 2015). The Institute of Medicine estimates that 116 million adults in the United States experience chronic pain, with direct and indirect annual costs totaling over half a trillion dollars (Institute of Medicine Committee on Advancing Pain Research, 2012). Low back pain (LBP) is the second most prevalent cause of disability in US adults and a common reason for lost work days with an estimated 149 million lost days of work per year (Freburger et al., 2011). The lifetime prevalence is as high as 79% in adults (Walker et al, 2004) and 84% in adolescents (Jeffries et al, 2007). The poor rates of recovery (58% at 1 month) and high rates of recurrence (73% in 12 months) contribute to high social and economic costs (Pengel et al., 2003). Chronic low back pain (cLBP) does not have a defined source, and the mechanism of development is not fully understood (Luedtke et al. 2015). In chronic pain the relationship between nociception and pain is often weak or lost indicating abnormal integration and recent neurobiological investigations corroborate the crucial role of the brain by showing substantial structural and metabolic changes (Pioner et al., 2016). It's been hypothesized that in the absence of a peripheral pathology, central sensitization contributes to the development and maintenance of non-specific chronic low back pain (Luedtke et al. 2015). The hypothesized mechanisms are an increased release of excitatory neurotransmitters at spinal level, influencing pain perception via the spinothalamic pathway and altered top down pain control from the brain (Luedtke et al. 2015). Chronic pain is currently extensively studied, but therapeutic options to date are limited, and duration of the symptoms tends to make pain increasingly resistant to treatment. Opioid therapy is helpful in the treatment of acute pain (Ferrari et al. 2015) limited evidence supporting its long-term effectiveness but a growing literature highlighting myriad risks of long-term use, including: misuse, abuse/dependence, overdose, and death (Chou et al., 2015). Deep brain stimulation has shown promising results, but less invasive forms of stimulation also might be effective (Antal et al., 2010). Some studies have shown that both a single session and repeated sessions of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) can relieve pain transiently in some patients with chronic pain (Naro et al., 2016, Antal et al., 2010), but others have found the effect to be small and not significant (Jimenez-Torres et al, 2016; Luedtke et al. 2015). Heart rate variability (HRV) is commonly used to assess the autonomic nervous system function and has been shown to predict poor health outcomes (Gockel et al, 2008). Initially developed to evaluate the prognosis of cardiac diseases (Balanescu et al., 2004), heart rate variability (HRV) analysis has been utilized to assess autonomic functions in chronic pain conditions (Staud et al., 2008, Kang et al., 2012). When compared to healthy controls individuals with chronic pain had lower HF (high frequency band) power in HRV representing less parasympathetic output in the altered cardiac autonomic regulation (Södervall et al., 2013). Gockel and colleagues (2008) found a significant association between heart rate variability and perceived

physical impairment in patients with chronic low back pain using Oswestry Disability Index scores. Patients with higher subjective disability had greater sympathetic dominance (lower high frequency band) than patients with minimal perceived disability.

2.2 INVESTIGATIONAL AGENT

One alternative not yet explored is Transcranial Alternating Current Stimulation (tACS). tACS is a safe, non-invasive, easy-to-administer procedure that applies weak electrical currents to the scalp to modulate rhythmic brain activity patterns. In addition, the Frohlich Lab has used this technology in clinical trials to treat individuals with serious mental illness, such as depression and schizophrenia (Frohlich 2015, Frohlich et al., 2016). Previous research has demonstrated that tACS enhances alpha oscillations in healthy participants (Zaehle et al., 2010) and may thus help to renormalize the presumed pathological structure of alpha oscillations in the pre-frontal cortex (PFC) of patients with chronic pain (Lustenberger et al., 2015).

Therefore, tACS may be an important next step in treating chronic pain. As stated above, some patients are resistant to other therapies including medications or in too much pain to do physical therapy. Treatment with tACS may provide an alternative for patients with disabling chronic pain who have few options.

2.3 DOSE RATIONALE

Previous studies have shown a relationship between alpha oscillations (8-12 Hz) and attention (Cooper et al., 2003), arousal, and emotion (Weinreich, Stephani, & Schubert, 2016; Gaeta et al., 2015). The substantial comorbidity of chronic pain and mental disorders and the close relationship between chronic pain and psychological factors indicates that brain dysfunction plays a central role in the development and maintenance of chronic pain (Pioner et al., 2016). Pain stems from dynamic interactions between sensory and contextual (i.e., cognitive, emotional, and motivational) processes that are mediated by feed-forward and feedback processes in the human brain. Alpha/beta oscillations are linked to the feedback process and a suppression of oscillations at alpha frequencies is associated with tonic pain. Previous studies in chronic pain have found an increase of theta oscillations, slowing of the peak alpha frequency, and increase in beta oscillations in the frontal areas (Lim et al., 2016). These changes along with the alpha-gamma oscillation coupling having a strong pain predictive model (Pioner et al., 2016) provide evidence alpha oscillations play an important role in chronic pain. Our proposed intervention of transcranial alternating current stimulation (tACS) at the alpha frequency (~10 Hz) has been shown to alter alpha oscillations with sustained effects (Kasten, Dowsett, & Herrmann, 2016). These data suggest that α -tACS at 10 Hz applied to the prefrontal cortex could potentially alleviate many of the symptoms associated with chronic pain. While there is currently no literature in HRV response to tACS, a study in progress is investigating HRV during tACS in healthy individuals. Since tDCS has been shown to increase parasympathetic and decrease sympathetic activity (Montenegro et al., 2011) we hypothesize that tACS will also increase parasympathetic activation specifically the high frequency bands.

2.4 STUDY AIMS/HYPOTHESES

2.4.1 PRIMARY OBJECTIVE

NULL HYPOTHESIS. There is no difference in parasympathetic tone in Heart Rate Variability, shown by an increase in high frequency input via spectral analysis on EKG recordings between active and sham stimulation.

ALTERNATIVE HYPOTHESIS. There is a difference in parasympathetic tone in Heart Rate Variability, shown by an increase in high frequency input via spectral analysis on EKG recordings between active and sham stimulation.

2.4.1 SECONDARY OBJECTIVE

NULL HYPOTHESIS. There is no difference in self-reported perceived pain rating between baseline and the active stimulation.

ALTERNATIVE HYPOTHESIS. There is a difference in self-reported perceived pain rating between baseline and active stimulation.

3 SUBJECT SELECTION AND WITHDRAWAL

A total of 20 participants will be recruited for this study and all data will be collected at UNC-CH. No specific plans have been made to enroll participants from vulnerable populations.

3.1 INCLUSION CRITERIA

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

- Provide signed and dated informed consent
- Male or female, aged 18-65
- Diagnosed with nonspecific chronic low back pain by clinician, normal MRI if they had imaging done
- BMI is less than 30
- Suffered from chronic pain for > 6 months
- Self-report pain measures (VAS) >4
- Meets criteria for low depression and suicide risk as defined by the HAM-D
- 1 month free anticonvulsant medications, 48 hours of opioids and benzodiazepines (can take over the counter pain killers)
- Can be taking over the counter pain killers not day of session (Refrain from taking over the counter medications such as antihistamines, albuterol, nasal decongestants for one week prior to stimulation sessions)
- Capacity to understand all relevant risks and potential benefits of the study (informed consent)
- Willing to comply with all study procedures and be available for the duration of the study
- Women of reproductive potential must test negative on a pregnancy test prior to start of treatment
- Speak and understand English

3.2 EXCLUSION CRITERIA

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

- Radicular Pain
- Diagnosis of eating disorder (current or within the past 6 months)
- Diagnosis of OCD (lifetime)
- ADHD (currently under treatment)
- Neurological disorders and conditions, including, but not limited to:
 - History of epilepsy
 - Seizures (except childhood febrile seizures and ECT-induced seizures)
 - Dementia
 - History of stroke
 - Parkinson's disease
 - Multiple sclerosis
 - Cerebral aneurysm
 - Brain tumors
- Medical or neurological illness or treatment for a medical disorder that could interfere with study participation (e.g., unstable cardiac disease, HIV/AIDS, malignancy, liver or renal impairment)
- Prior brain surgery

- Any brain devices/implants, including cochlear implants and aneurysm clips
- Traumatic brain injury
- (For females) Pregnancy or breast feeding
- 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

Justifications for any exclusions based on race, gender, or ethnicity: Non-English speaking individuals are excluded because the ability to accurately and completely communicate study information, answer questions about the study, and obtain consent are necessary.

Justification for excluding women or women who become pregnant: Pregnant participants will be excluded despite the fact that theoretical risk to mother or fetus is exceedingly small, since no safety data for pregnancy is known to exist for tDCS/tACS studies. We will verify pregnancy status via a urine pregnancy test for all female participants prior to receiving treatment on Day 1 of Stimulation.

3.3 STRATEGIES FOR RECRUITMENT AND RETENTION

3.3.1 RECRUITMENT

This clinical trial will utilize multiple recruitment strategies in order to communicate this opportunity to as many potential participants as possible. Participants will be recruited from the following sources using IRB approved flyers and email scripts:

- UNC University Physical Therapy clinic locations
- UNC Hospital and Carolina Data Warehouse
- North Carolina Institutions of Higher Learning

The UNC community will also be notified of the study through the informational notify.unc.edu system and a research listing will be created on <http://allyresearch.org/> as well as on <http://jointheconquest.org>. A short description of the study will also be included on the Frohlich lab website. We will also have a posting on the Frohlich lab website.

The prevalence of chronic LBP in North Carolina has increased from 1992 to 2006 as it more than doubled in the 14 year interval from 3.9 to 10.2 percent (Freburger et al., 2009). Studies have also documented increases in visits to physicians, physical therapists, and chiropractors (Martin et al., 2008). UNC Healthcare has a chronic pain clinic as well multiple physical therapy locations allowing local access to a large chronic pain population.

3.3.2 RETENTION

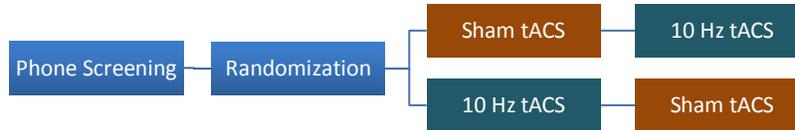
Our retention strategy includes a payment schedule of two times per participant. The participant will receive payment on both days of stimulation. The research staff will also give each participant a reminder call or email for the day 1 of stimulation and day 2 of stimulation. Each research staff member 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 to establish rapport and encourage the participant to continue attending sessions. The study team will work hard at forming a professional relationship with each participant so that 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).

4 BASIC STUDY DESIGN

This study is a pilot clinical trial with a randomized, double-blind, crossover design. This is a single site study with 2 arms. We estimate six months to complete study enrollment.

Figure 1.



Active sham treatment will include 10 seconds of ramp-in to 1 minute of 10 Hz tACS with a ramp-out of 10 seconds for a total of 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. 10 Hz tACS will have a 10 second ramp-in and ramp-out with 40 minutes of stimulation for a total of 2420 seconds of stimulation. Stimulation waveform is a sine-wave with peak-to-peak amplitude of 2 mA. In both arms, participants will stay in a relaxed yet controlled state by watching a nature movie (“Reefscape”) during stimulation.

Eligible participants who complete this clinical trial will have a total of 2 visits; 2 days of stimulation (with 1-3 weeks in between). Day one of stimulation will take approximately 2.5 hours as eligibility will be confirmed at the beginning. Day 2 of stimulation will take approximately 2 hours. Two days after each stimulation day, participants will receive via email a follow-up survey to complete that will take approximately 15 minutes. We estimate that total participation will be approximately 6 hours over the course of 6 weeks. All time estimates take into consideration breaks and time variance in administration.

4.1 TREATMENT ASSIGNMENT PROCEDURES

Participants will be randomized into one of 2 arms (*see Figure 1 above*). This is a double-blind study, so neither the participant nor the research will know which treatment the participant is receiving, if any.

4.1.1 RANDOMIZATION PROCEDURES

Charles Zhou will randomize 6-digit stimulation codes which will be used by the study coordinator and research assistants and will be linked to the participant numbers of enrolled participants. These stimulation codes are directly linked to which treatment participants receive (sham or 10 Hz tACS) and will be used with the XCSITE100 stimulator. An unblinded code sheet that matches these stimulation codes to treatment arm will be kept by Charles Zhou and will not be available to the study coordinator or research assistants.

The unblinded code sheet will have the following information:

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

A copy of this code sheet with condition number and condition name REMOVED is provided to the study coordinator and research assistants. This blinded code sheet will be used to ensure the correct stimulation code is provided for each session.

These linked codes ensure that the study coordinator and research assistants are kept blinded to which treatment each participant receives. Please see *Data and Safety Monitoring* for more information on unblinding this information.

5 STUDY SCHEDULE

In order to increase data quality, the assessments for an individual participant will be administered by the same researcher.

It is important to note that consent, scales, and experiments will all take place in a private room. Any phone calls will take place in a private lab environment as well.

5.1 SCREENING

The screening process has been divided into two steps: phone screening and an initial session. The phone screening allows researchers to screen out participants based on self-report responses and for potential participants to become familiar with the study schedule, including procedures. The initial session allows researchers to confirm any preliminary diagnoses and assess for exclusion criteria that cannot be confirmed via phone.

5.1.1 SCREENING TELEPHONE CALL

During the telephone screening, researchers will provide a brief background about chronic pain and tACS. The timeline of visits will be explained, including the number of visits and the time commitment required. The participant will be informed of compensation, both amount and payment schedule. The participant will be asked if they have any questions. Once all questions have been answered, the participant will be asked if he/she is still interested in participating in the study. If yes, the researcher will ask if the participant will provide verbal consent to begin the initial phone screening which will determine eligibility for the initial session. *A telephone script, which includes the screening questions, is provided in Appendix G.* If the participant meets initial criteria with these two assessments, the initial session will be scheduled and a reminder call or email will be given at least 24 hours before the initial session.

5.1.2 INITIAL SCREENING SESSION (VISIT 1)

At day 1 of stimulation, participants will be guided through the consent form and the HIPAA authorization form and be given the time to ask any questions about the information discussed. To ensure that all aspects of the research are understood, participants may be asked a series of questions about the research they are about to take part in (*Appendix E*). Once it is clear that the participant understands the consent form and HIPAA authorization, they may sign the forms.

Following the consent process, the participant completes the ODI and DVPRS to measure disability and pain intensity on 0-11 scale. The HAM-D and DASS-21 will assess low suicide risk and depression level. The self-report measures: UCLA Activity Score, PCS, and PSEQ will assess physical activity limitations, pain experience, and confidence in daily activities. Data on demographics, handedness, stai, bis-bas, and opinion pre-treatment will also be collected.

Once eligibility has been confirmed and all relevant data collected, Day 1 of stimulation will begin.

5.2 STIMULATION SESSIONS

5.2.1 DAY 1 OF STIMULATION (VISIT 1 CONTINUED)

Prior to starting any study procedures, female participants will be asked to take a urine pregnancy test to ensure continued eligibility. The 5xSST, FTF, and pressure pain threshold test will be administered before stimulation. A resting state EEG will be recorded for 5 min before and after stimulation. The participant will receive 40 minutes of sham or 10 Hz tACS stimulation (as per the initial randomization) while watching “Reefscape”. The stimulation will be followed by the pressure pain threshold, 5xSST, FTF, stimulation adverse effects questionnaire and perceived improvement ending the session.

5.2.2 DAYS 2 OF STIMULATION (VISIT 2)

Prior to starting any study procedures, female participants will be asked to take a urine pregnancy test to ensure continued eligibility. The ODI, DVPRS, 5xSST, FTF, and pressure pain threshold test will be administered before stimulation. A resting state EEG will be recorded for 5 min before and after stimulation. The participant will receive 40 minutes of sham or 10 Hz tACS stimulation (as per the initial randomization) while watching “Reefscape”. The stimulation will be followed by the pressure pain threshold, 5xSST, FTF, stimulation adverse effects questionnaire and perceived improvement ending the session.

5.3 FOLLOW-UP

5.3.1 FOLLOW-UP EMAIL

Two days after both sessions of stimulation, participants will receive an email with a follow up survey to assess any change in pain perception. The ODI and DVPRS will take approximately 15 minutes to complete.

5.3.2 UNBLINDING PROCEDURES

There are no current plans to systematically unblind participants to the treatment they may or may not have received during the clinical trial. However, following the completion of data collection, participants may contact the Frohlich Lab for unblinding information.

6 STUDY PROCEDURES/EVALUATIONS

6.1 SELF-REPORT MEASURES

During the initial session, researchers will collect demographics, which include medical history and medication history. In addition, several other self-report measures will be used throughout this study. These measures are listed below and can be found in the attached documents.

- A. OSWESTRY DISABILITY INDEX (ODI) is a 10 item self-report assessment to measure level of disability and monitor change over time. It takes only 5 minutes to complete with a MCID of 10 pts. (Fritz et al., 2001)
- B. DEFENSE AND VETERANS PAIN RATING SCALE (DVPRS) is a modified numeric rating scale with faces and word descriptors. The MCID is 2 pts. It also includes supplementary questions on the impact of chronic pain on other aspects of daily living (Buckenmaier et al., 2013).
- C. UCLA ACTIVITY SCORE is a self-report measure of 1 question to measure activity level and change.
- D. PAIN CATASTROPHIZING SCALE (PCS) is a 13 item self-report measure designed to quantify an individual's pain experience.(Sullivan et al., 1995)
- E. PAIN SELF-EFFICACY QUESTIONNAIRE (PSEQ) is a 10-item questionnaire measuring confidence in ability to perform specific tasks or coping with pain (Nicholas, 2007)
- F. DEPRESSION ANXIETY STRESS SCALE (DASS-21) is a 21 item short form self-report questionnaire (Original DASS is 42 items) that provides a quantitative measure of depression, anxiety, and stress experienced in the past week. It is important to note that the DASS-21 is not a diagnostic tool (Lovibond & Lovibond, 1995).

6.2 CLINICAL MEASURES

In addition to self-report measures, several clinical measures will be used throughout this study, both for measuring change over time and for diagnostic use. These measures are listed below and can be found in the attached documents.

- A. HAMILTON PSYCHIATRIC RATING SCALE FOR DEPRESSION (HAM-D) is a 21-item assessment to rate the severity of depression in patients (Hamilton, 1960). This measure is being used to assess levels of depressive symptoms and to determine suicide risk. Low suicide risk for this study is defined as scoring 2 or less on the Suicide question on this assessment.
- B. FIVE TIMES SIT-TO-STAND TEST (5xSST) is a quick and easy to administer test of an individual's ability to transition between sitting and standing five times in a row and has been previously tested in chronic LBP populations. We will use as a measure of functional lower limb muscle strength and in quantifying functional change of transitional movements with MCIS between 4-9 seconds (Simmonds et al., 1998, Andersson et al., 2010) .
- C. FINGERTIP-TO-FLOOR TEST (FTF) is a valid, reliable, and responsive test in individuals with chronic low back pain. It measures trunk flexion and the MCIC varies (approx. 10 cm) (Perret et al., 2001)

6.3 SPECIAL ASSAYS OR PROCEDURES

6.3.1 SPECIAL PROCEDURES

Each participant will attend two days of stimulation for this study. Each participant will be randomly assigned to one of two treatment arms (sham or 10 Hz tACS) then the opposite on the second visit. For more information on the stimulation procedures, see section 7.2 *Preparation and Administration of Study Investigational Product*.

6.3.2 EKG PROCEDURES

To obtain a measure of the heart rate during both stimulation conditions, ECG electrodes as part of the EEG acquisition system are placed on the participant's body. Ideally one electrode will be placed below the left collarbone and a second below the right chest. The EKG will be recorded for the full 40 minutes stimulation session during spontaneous breathing and will be divided into 10 minute intervals for analysis. A standard spectral analysis will be applied to a 10-minute interval, including total power, HF, LF, and VLF. The HF component reflects the parasympathetic modulation of the heart rate.

6.3.3 PRESSURE PAIN THRESHOLD

The Wagner FDX Algometer will be used for the pressure pain threshold test. Algometers are designed to quantify and document levels of pain sensitivity via pain tolerance measurement. Pressure algometry is a reliable measure of pain in muscle, joints, tendons, and ligaments

Pressure will be applied on both forearms and on the place of most pain on the lower back. The assessment will be done three times in a row at each location and the average of the trials will be used.

EEG PROCEDURES

In addition, in order to detect any change(s) at the neurophysiological level, a resting state EEG will be recorded before and after stimulation during both sessions. This measurement will contribute to the design of novel network-level biomarkers of chronic pain and of response to pain.

6.4 SAFETY MEASURES

We will be monitoring the safety of our participants throughout the study with the following measures. These measures are listed below and can be found in the attached documents.

- A. A stimulation adverse effects questionnaire used in previous studies (IRB #14-1622, #14-3285, and #14-0600) will be administered at the end of each stimulation session. This questionnaire will be used as a safety measure and to collect data on participant experience. Please see *10.1 Safety Parameters* for more information.
- B. More as needed. Refer to previous IRB applications as needed.

6.5 LABORATORY EVALUATIONS

6.5.1 SCREENING LABORATORY EVALUATIONS

A urine pregnancy test will be performed for any female participant who is unable to confirm pregnancy status.

INSTRUCTIONS FOR SPECIMEN PREPARATION, HANDLING, AND STORAGE. For this laboratory evaluation, results are available after only a few minutes. Once the results are clear, the researcher will make a note and the sample will be disposed. All samples will be handled using single-use disposable medical gloves.

6.5.2 SALIVA SAMPLE

We will be collecting a saliva sample during the first visit. This sample will be used to test for a single nucleotide polymorphism in the BDNF gene whose presence may have an influence on effectiveness of brain stimulation. Within the central nervous system, BDNF regulates survival, proliferation, and synaptic growth as well as directly influences synaptic plasticity in the adult human brain (Antal et al., 2010a). Egan et al. (2003) demonstrated that Val66Met, a single nucleotide in the BDNF gene, has function consequences in healthy humans, including decreased episodic memory and hippocampal inducing a reduction in recall capacity. This polymorphism is common in over one third of the Caucasian population (65% Val66Val to 35% Val66MET) (Pezawas et al, 2004; Hariri and Weinberger, 2003). Kleim et al. (2006) found that individuals with the Val/Val polymorphism respond to tDCS and transcranial magnetic stimulation (TMS) treatments with expected change, whereas, individuals expressing Val/MET allele do not. These authors indicate the difference to be caused by the impairment in synaptic plasticity caused by the Val/MET allele. These findings suggest that individual efficacy of treatments using brain stimulation may be partially genetically predetermined and should be taken into account when performing such procedures. Accordingly, we will conduct genotyping of all participants in this study in order to assess BDNF status. We will perform exploratory analyses in which we group participants by BDNF status. A saliva sample will also test for levels of progesterone, estradiol,

INSTRUCTIONS FOR SPECIMEN PREPARATION, HANDLING, AND STORAGE. The saliva sample will be collected using 2mL DNA collection kit from DNA Genotek. Before sample collection, it is imperative that the participant does not eat, drink, smoke or chew gum for at least 30 minutes before providing a sample. Once the participant provides the 2mL sample, the collection tube is closed and a liquid from the lid will be released into the tube. The original lid will be removed and replaced with a small cap and the tube will be agitated for 5 seconds. The sample is then returned to the plastic packaging and labeled with the date of collection, the study name, and the participant ID. These samples are kept in a secure location until the completion of data collection.

7 STUDY INVESTIGATIONAL PRODUCT

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

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

The stimulator has two main components:

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

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

7.1 SAFETY FEATURES

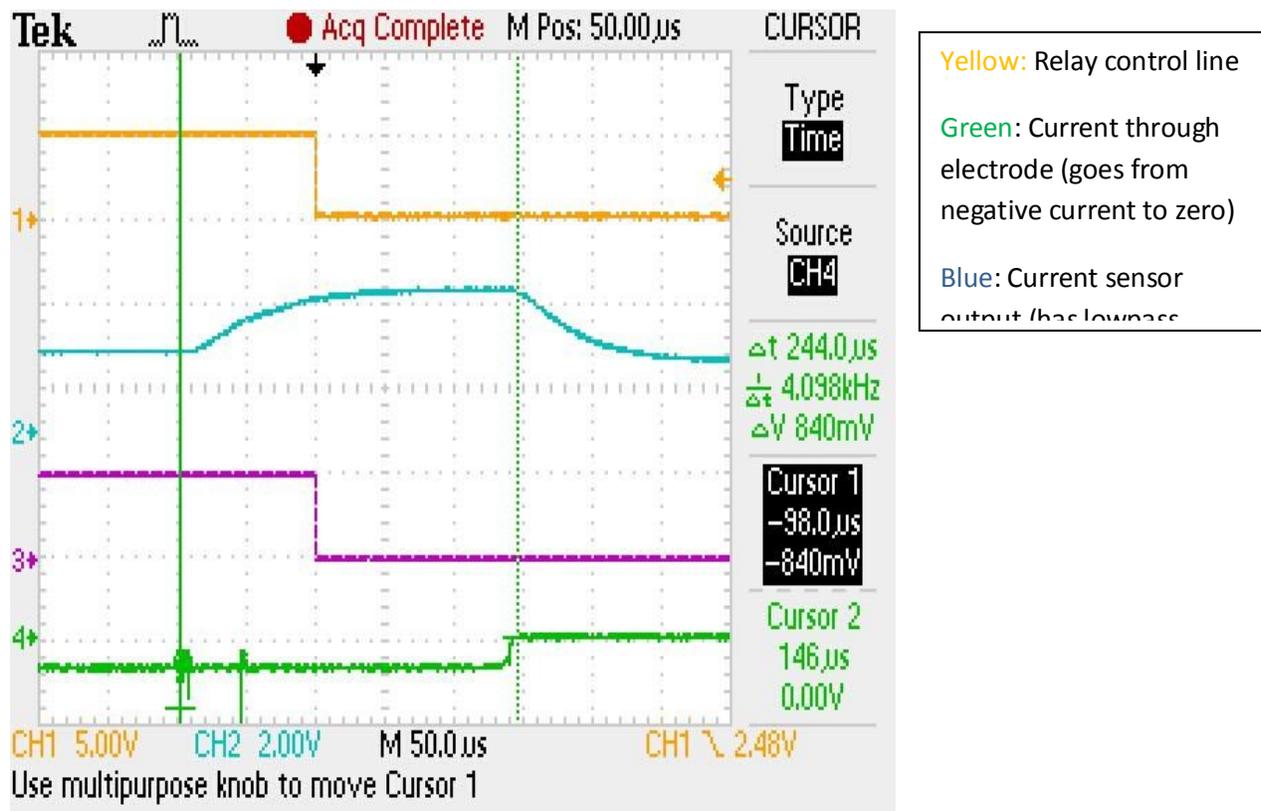
Current Sensor Circuit. A 33.2 Ω sense resistor is placed in series with the stimulation electrodes on the high side. Since high-side current sensing is used, any short circuit of the electrode terminals to ground will be detected. The stimulation current flows through this resistor and creates a voltage.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

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

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

1. **AUTOMATIC SOFTWARE CURRENT CUTOFF.** The output of the current sensor described above is read by a microprocessor, which compares the reading to a value of ± 3 mA peak. If the current exceeds these limits, stimulation is stopped, a relay in series with the electrode is opened, and the power supply used for stimulation is turned off. The user is then given the option to investigate the issue, and cancel or resume the test. Since high-side current sensing is used (described above), any short circuit of the electrode terminals to ground will be detected.
2. **AUTOMATIC HARDWARE CURRENT CUTOFF.** The output of the current sensor is fed into a pair of comparators which detect if the current exceeds ± 4.5 mA. If so, the fault is latched such that the relay in series with the electrodes is opened. Additionally, the microprocessor is notified of this instance through an interrupt. Upon this interrupt, the microprocessor immediately stops stimulation and the power supply used for stimulation is turned off.

Figure 1. Example of a successful hardware cutoff function



3. **PERMANENT HARDWARE CURRENT CUTOFF.** A 5 mA fast-acting fuse is in series with the electrode connector. If the above two over-current detection methods fail, the fuse will blow, and the stimulator will no longer be electronically connected to the device.
4. **POWER SUPPLY FUSE.** Finally, if for no other reason the entire device draws too much current, the main power supply fuse is blown. This fuse is sized with a cutoff of 200% of steady-state operating current.

7.2 PREPARATION AND ADMINISTRATION OF STUDY INVESTIGATIONAL PRODUCT

After participants have completed the daily questionnaire, they will be comfortably seated. The researcher(s) will first measure their head using the 10-20 system for accurate electrode placement. Participants will then be fitted with the 3 electrodes for stimulation. Electrodes will be applied using Ten20 conductive paste, 5x5cm electrodes placed over F3 and F4 with a 5x7cm placed over CZ as a return electrode. The participant will be in a relaxed yet experimentally controlled state by watching "Reefscape". One session of stimulation will be performed per day for 40 minutes. For the 10 Hz tACS stimulation, there will be a 10 second ramp-in and ramp-out with 40 minutes of stimulation for a total of 2420 seconds. Stimulation waveforms are sine-waves with a peak-to-peak amplitude of 2 mA. The sham stimulation will include 10 seconds of ramp-in to 1 minute of 10 Hz tACS with a ramp-out of 10 seconds for a total of 80 seconds of stimulation. As a covariate, heart rate will be recorded throughout stimulation.

Stimulation devices will be programmed and codes will be randomized to one of the two experimental arms. Researchers will enter the participant-specific code into the App that controls the stimulation and monitor participants during the 40 minutes of 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, a daily questionnaire will be administered after each stimulation session.

7.3 ASSESSMENT OF PARTICIPANT COMPLIANCE WITH STUDY INVESTIGATIONAL PRODUCT

Compliance for this study includes making both stimulation sessions. Participants have the ability to schedule their second stimulation 1-3 weeks after the first. Follow-up emails will be sent out 2 days after scheduled visit.

8 POTENTIAL RISKS AND BENEFITS

8.1 BENEFITS TO SUBJECTS AND SOCIETY

Chronic pain is a debilitating disorder that involves problem in the feedback (top-down) mechanism in pain processing. Our novel approach introduces non-invasive brain stimulation for brain dysfunction and has the potential to treat symptoms not only in chronic pain, but also in depression and schizophrenia (Frohlich, 2015; Frohlich et al., 2016). Additionally, tACS has the potential to provide a treatment option that is safe, scientifically-supported, low-cost, easy-to-administer method to effectively reduce symptoms in patients suffering from chronic pain. The chance to understand and develop a new treatment for chronic pain is an important step in helping the millions of people in the world who suffer from its effects, from physical handicaps to common psychiatric comorbidities including opioid addictions and depression. If tACS is feasible and effective for patients with chronic pain, findings will provide persuasive preliminary results for the National Institutes of Health (NIH) and National Institute of Mental Health (NIMH) proposals to fund a large-scale clinical trial for patients with this serious disorder.

This study has not been designed to benefit the individual participants. However, participants in this study may experience some degree of relief from chronic pain symptoms as a result of tACS treatment. There are no serious risks to the participant from the treatment used in this study.

8.2 POTENTIAL RISKS

8.2.1 PSYCHOLOGICAL

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

Risk of Confidentiality. All subjects will be informed during the consent process that if they report violent or suicidal ideation/behavior, this information will be kept confidential unless the subject reports a plan to hurt themselves or an identified victim. In this case, appropriate referrals will be made and the subject will be advised to end their participation in the study.

In the unlikely event of a breach of confidentiality, people might discover that an individual was involved in this research study. Some people 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, 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 participating 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 participating training that includes education about responsibilities to minimize the risk of confidentiality breach.

8.2.2 PHYSICAL

Risk of Injury and Discomfort: Transcranial current stimulation has been used without any reports of serious side-effects for more than a decade. This stimulation made has NOTHING to do with electroconvulsive therapy that applies many orders of magnitude higher stimulation current. Rather, transcranial current stimulation is so weak that it does not cause super-threshold activation of neurons (Frohlich and McCormick, 2010). In particular, tACS has been used without reports of any serious side-effects. Some participants report a transient mild tingling, burning, or itching underneath the electrodes and headache, but no other side effects have been noted. Importantly, it remains unclear if these mild side-effects were caused by the transcranial brain stimulation. In order to monitor these side-effects, we will be administering an adverse effects stimulation questionnaire after each stimulation session to determine whether these effects were experienced. Research personnel present during these sessions will also check in with the participant periodically during the stimulation to see whether they are comfortable. If any side-effect occurs (rated by the participant as stronger than “moderate”) or the participant is experiencing severe discomfort, the stimulation will be immediately stopped.

8.3 REFERRALS FOR MEDICAL FOLLOW-UP OR PSYCHOLOGICAL COUNSELING

There is a purely theoretical likelihood that stimulation of neuronal circuits can lead to epileptic discharge. To minimize this occurrence, we screen and exclude patients with personal and family history of neurological conditions from the study. If abnormalities or a seizure is witnessed during the course of the study, a referral will be made to the UNC Department of Neurology for follow-up. In the theoretical event that a seizure is witnessed that involves the loss of consciousness, the patient will be told not to operate a motor vehicle until cleared by the DMV.

We will be using the Hamilton Psychiatric Rating Scale for **Depression** (HAM-D) to assess depression and suicide risk at the initial session. Inclusion criteria states that the patient must be low suicide risk, potential participants that have an above “low risk” designation that is currently clinically relevant will not be eligible for the study.

To ensure participant comfort, a study coordinator or research assistant will periodically check in with the participant about any side-effects he/she may be experiencing during each stimulation session. Following the conclusion of the stimulation session, the participant will receive an Adverse Effects Questionnaire to report on any of the side-effects he/she may have experienced. This questionnaire reports side-effects on a likert scale (1=Absent, 2=Mild, 3=Moderate, 4=Severe). If the participant reports side-effects of Moderate to Severe intensity, a study coordinator or research assistant will discuss the side-effects experienced and note this response. The medical monitor will be contacted based on the reported intensity on the Adverse Events Questionnaire and the participant’s verbal confirmation of intensity.

8.3.1 PREGNANCY FOLLOW-UP

Every female participant will take a pregnancy test on Day 1 of Stimulation. If, after testing negative at Day 1 of Stimulation (meeting inclusion criteria), a participant reports becoming

pregnant during the course of the study, she will be withdrawn from further participation. There are no plans to follow participants who become pregnant while enrolled in the study.

9 DATA AND SAFETY MONITORING

9.1 FROHLICH LAB MONITORING PLAN

The purpose of this monitoring plan is to present the Frohlich Lab's approach to monitoring clinical trials. The plan facilitates compliance with good clinical practice (GCP):

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

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

The latest version of the approved IRB application for this clinical trial will be followed at all times. This responsibility falls into the hands of the study coordinator and research assistants. If at any time there is a deviation from protocol, the deviation from protocol log will be filled out. All team members will be trained on how and when to use this log. The most up-to-date IRB application will be on file in the Clinical Trials office in Room 233 of the Medical School Wing C. Deviations will be sent to the IRB every 4-6 weeks (if necessary).

Periodically, study staff should review 3 randomly selected informed consent forms to ensure that (1) these forms have been filled out appropriately, and (2) the consent form process was followed and properly documented. Should any consent form be in violation, the research team will perform and document a complete review of all consent forms.

AE and SAE are clearly defined in this document. Documents of AE and SAE can be found in the study binder on file in the Clinical Trials office in Room 233 of the Medical School Wing C. It is the responsibility of the study coordinator to report all events to the PI in a timely manner (see 9.3 *Reporting Procedures*). All AEs and SAEs will be discussed with the PI. For our practices, we have adapted the decision tree provided by the UNC-CH IRB to assist with reporting of such events.

Periodically, the study coordinator should also choose one CRF/eCRF and Source Document to assess for completion and maintenance. In addition, the PI will assess completeness of data on REDCap. The PI has read-only access. This allows the PI to view reports that provide information on any missing data on an individual participant basis, but does not allow the PI to add, change, or input any data.

A data safety monitor will review blinded AEs every month. The DSMB will assess recruitment and will only evaluate safety if an unanticipated concern arises.

9.3 EARLY WITHDRAWAL OF PARTICIPANTS

9.3.1 REASONS FOR WITHDRAWAL

A study participant will be discontinued from further participation if:

- The participant meets any exclusion criteria (either newly developed or not previously recognized).
- Anything that, in the opinion of the investigator, would place the participant at increased risk or preclude the participant's full compliance with or completion of the study.

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

9.3.2 DATA COLLECTION AND FOLLOW-UP FOR WITHDRAWN PARTICIPANTS

We will collect safety data on any participant discontinued because of an AE or SAE. In any case, every effort will be made to undertake protocol-specific follow-up procedures. If voluntary withdrawal occurs, the participant will be asked to continue scheduled evaluations and complete an end-of-study evaluation. If an AE has been reported, researchers will help the participant seek the medical care they need and a follow-up will be performed by the PI and Co-I. In the case of an early withdrawal, the researcher will make a note to file indicating this.

9.4 TERMINATION OF STUDY

If a seizure occurs at the time of a study visit, a temporary hold will be placed over the study and further investigation will ensue. This could lead to stopping the study prematurely or continuing on with further safety measures in place. If two seizures are witnessed during the study visits, the entire study will be stopped prematurely. These individuals would be referred for further medical attention. It is very unlikely that a seizure will occur, given that previous studies using tDCS in patients with depression and schizophrenia have had no seizures occur (Berlim et al., 2013).

The study will also be stopped (at least temporarily) if studies provide evidence that transcranial current stimulation caused brain damage or other harmful effects on subjects, either short-term or long-term. Examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events.

The reasons for stopping the study and asking for further investigation include:

- Increased pain due to treatment (>25% of participants asked to seek additional health care)
- If a seizure occurs during a study visit, a temporary hold will be placed on the clinical trial

The IRB will also be informed promptly and provided the reason(s) for the termination of suspension of by the investigator, as specified by the applicable regulatory requirement(s).

10 SAFETY & REPORTING

It is important to assess safety over the course of this study. This section describes in detail how safety is assessed, reporting of Adverse Events, Serious Adverse Events, and Unanticipated Problems. This section is a reference for internal use.

10.1 SAFETY PARAMETERS

SUICIDE RISK. Participants with high suicide risk (SI or SB) will be excluded from our study.

STIMULATION SIDE EFFECTS. A stimulation adverse effects questionnaire used in previous studies will be administered at the end of each stimulation session and at the 4 week follow-up visit. This questionnaire will be used as a safety measure and to collect data on participant experience. The adverse effects questionnaire asks participants to respond on a 4 point likert scale on the severity of symptoms experienced during the stimulation session (1 = absent, 2 = mild, 3 = moderate, 4 = severe). The side effects listed are headache, neck pain, scalp pain, tingling, itching, ringing/buzzing noise, burning sensation, local redness, sleepiness, trouble concentrating, improved mood, worsening of mood, dizziness, flickering lights, and other (specify). Participants are also asked to rate on a 5 point likert scale how related they believe the side effects to be to stimulation (1 = no relation, 2 = remote, 3 = possible, 4 = probable, 5 = definite).

In addition to this survey, the study coordinator or research assistant will periodically check in with the participant during the stimulation session to assess side effects.

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

10.2.1 ADVERSE EVENTS

All AEs, including local and systemic reactions not meeting the criteria for “serious adverse events”, will be captured on the appropriate CRF. In addition, the AE Report Form will be completed by the study coordinator (Appendix B). The AE Report Form includes the following:

- What is known about the therapy
- What is known about previous reported side effects
- If the AE occurred in temporal relation to the therapy
- Whether or not the AE improves or disappears when treatment is stopped
- Whether the AE is worsening of baseline symptoms
- Whether the AE is related to concurrent medical condition or medication use

Once complete, this form will be given to the PI and Co-I, who will review, comment, and sign this form. Completed forms will be placed in the participant’s folder.

In addition, the study coordinator will document any AE occurrence on the AE log (*Appendix D*), which includes information such as the date of the AE, severity, relationship to the treatment (assessed by the PI and Co-I*), actions taken, and outcome(s). The log will be reviewed and

initiated by the PI 72 hours after being completed. All AEs occurring during the clinical trial will be documented appropriately regardless of relationship to tACS. All AEs will be followed to adequate resolution and will be graded for severity and relationship to study treatment. Any medical condition noted at the initial session will be considered at baseline and not reported as an AE.

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

- **ASYMPTOMATIC.** The participant is exhibiting no symptoms due to this event; no treatment needed.
- **MILD.** Event results in mild or transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily activities (e.g., insomnia, mild headache)
- **MODERATE.** Event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (e.g., fever requiring antipyretic medication). In the case of a moderate AE, the medical advisor may recommend an over the counter medication.
- **SEVERE AND UNDESIRABLE.** Event results in significant symptoms that prevent normal daily activities; may require hospitalization or invasive intervention (e.g., anemia resulting in blood transfusion).

Changes in the severity of an AE will be documented with the Note to File document (Appendix E) and will be filed in the participant's folder.

***Relationship to Study Products:** The PI and Co-I will together determine whether an AE is associated with the study treatment. The event will be labeled associated if the event is temporally related to the administration of a therapy and no other factors can explain the event. The event will be labeled as not associated if the event is temporally independent of the study treatment and can be explained by external factors, such as major life events.

10.2.1 SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE): An SAE, as defined by the NIH, consists of adverse events that result in death, require either inpatient hospitalization or the prolongation of hospitalization, are life-threatening, result in a persistent or significant disability/incapacity or result in congenital anomaly/birth defect. Other important medical events, based upon appropriate medical judgment, may also be considered Serious Adverse Events if a trial participant's health is at risk and intervention is required to prevent an outcome mentioned.

All SAEs will be recorded on the Serious Adverse Events Form (Appendix B), documented in the UE/SAE log and reported to the IRB. The SAE Form will be completed by the study coordinator, and includes information relating to the onset and nature of the SAE, relationship to the study treatment, seriousness of the SAE, treatment required as a response to the SAE, and outcome. This form will be filed in the participant's folder at the resolution of the event. The study coordinator will complete the UE/SAE log (Appendix D) which includes information such as the date of the event, time at which the study team was informed of the event, details, when the IRB was notified, and the date that the SAE form was completed.

10.2.2 UNANTICIPATED PROBLEMS

Unexpected Events (UE) will be recorded on the UE/SAE log (Appendix D) and will include information such as the date of the event, when the study team was informed of this event, details of the event, when the IRB was notified, and whether the SAE form was completed. The IRB will be notified of each UE that may occur during the study.

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

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (in the guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

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

10.3 REPORTING PROCEDURES

We will be adopting the following table for reporting procedures:

What Event is Reported	When is Event Reported	By Whom the Event is Reported	To Whom the Event is Reported
Fatal or life-threatening unexpected, suspected serious adverse reactions	Within 24 hours of initial receipt of information	Investigator	Local/internal IRBs
Non-fatal, non-life threatening unexpected, suspected serious adverse reactions	Within 48 hours of initial receipt of information	Study Coordinator	Local/internal IRBs/Institutional Officials, DSMB
Unanticipated adverse device effects	Within 10 working days of investigator first learning of effect	Investigator	Local/internal IRBs
Unanticipated problem that is not an SAE	Within 7 days of the investigator becoming aware of the problem	Investigator	Local/internal IRBs/Institutional officials
All Unanticipated	Within 30 days of the	IRB	OHRP

Problems	IRB's receipt of the report of the UP from the investigator	Investigator	External IRBs
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10.3.1 REPORTING OF PREGNANCY

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

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

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

11 STATISTICAL PLAN

11.1 STATISTICAL ANALYSIS STRATEGIES

Our study design is a AB/BA crossover and we will ensure a washout effect by scheduling 1-3 weeks between stimulation sessions. A continuous outcome approach will be used to analyze the crossover trial data where carryover effects will be assumed to be equal.

Primary outcome: Use kubios software to analyze HRV over before and after stimulation. A standard spectral analysis will be applied to the pre and post intervals, including total power, HF, LF, and HP. Specifically looking at the HF component since it reflects the parasympathetic modulation of the heart rate. Use a repeated measure ANOVA with factor session (1 vs 2) and factor treatment (active vs sham) (R software). We hypothesize a treatment main effect and with no session effect and no interaction.

Secondary outcome: A Mann-Whitney-Wilcoxon rank-sum testMann Whitney U test (R software) will be performed on the self-report VAS pain scale (nonparametric scale) (from DVPRS) before and after stimulation as well as between sessions to analyze any differences in self-report perceived pain. Grouped ANOVAs and unpaired t-tests may also be used to analyze correlations within other self-report measures

11.2 SAMPLE SIZE DETERMINATION

This clinical trial represents a pilot study. A pilot study is a clinical trial that is conducted to decide whether a new treatment should be tested in a large controlled trial; therefore, we do not calculate sample size. This study can be considered a pilot study, as it is the first time this specific treatment will be performed on this clinical population. The results from this study will be used to determine sample sizes for future, large-scale clinical trials. In addition, we have to restrict the number of included participants to a small sample size due to limited funding resources.

11.3 DATA MANAGEMENT

Data will be stored in a password-protected cloud-based data system that does not contain any patient information. Individual records are referred to by dummy identifiers that cannot be traced back to the study participants except with the master code list that is stored separately in a secured location.

12 DATA HANDLING AND RECORD KEEPING

The study coordinator and research assistants are responsible for the accuracy, completeness, legibility, and timeliness of the data reported.

12.1 PHI AND HIPAA

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from the participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

12.2 CONFIDENTIALITY

To ensure confidentiality, all data will only be referenced by a dummy identifier. Source documents (i.e. paper forms) will be kept in a locked file cabinet in a locked office. In addition, all data will be stored on a password-protected computer using a password-protected data collection tool (REDCap). The key linking dummy identifiers with participant information will be securely located separate from all other data collected.

12.2.1 ACCESS TO SOURCE DOCUMENTS

The research coordinator, research assistants, and PI will have access to all of the source documents collected over the course of the study. The Co-I and medical monitor will have access to files upon request, as they will need access to the locked rooms and filing cabinets in which these documents are located.

Data will stay on a password-protected computer. Subsequently, a copy will be processed on a separate, password-protected desktop computer in the Frohlich Lab (Neuroscience Research Building 4129).

12.2.2 SENSITIVE INFORMATION

Sensitive information will be collected in this study, including information about medical conditions and drug use. We are using the DASS-21 and HAM-D to assess comorbid depression and ensure that the participant meets eligibility criteria (low suicide risk).

12.2.3 OTHER

Please note that there is no significant risk of deductive disclosure in this study. In addition, none of the groupings or subgroupings used in analysis will be small enough to allow individuals to be identified.

12.3 SOURCE DOCUMENTS

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source data include:

PARTNERS HUMAN RESEARCH COMMITTEE (IRB).

- All IRB correspondences are documented
- The study staff is IRB approved prior to performing any study procedures
- Adverse events and deviations are reported to the IRB per current guidelines and stored appropriately
- All versions of the IRB protocols and informed consent forms are on file

INFORMED CONSENT.

- Ensure that participant identification is not recorded on the ICF (i.e., no participant ID)
- There is documentation that the participant is given a copy of the consent form
- The participant and study representative signed and dated the consent form for him/herself
- The participant initialed and dated all appropriate pages on the informed consent form
- Note to file (Appendix F) made for any informed consent deviations
- Ensure a valid (current version date) copy of the consent form was used

PROTOCOL DEVIATIONS.

- Any and all protocol deviations (exceptions and violations) are documented in the participant folder and reported to the IRB as required

OTHER SOURCE DOCUMENTS.

- Each participant folder will contain a checklist to ensure that all source documents are administered and collected properly. The checklist will be dated by the researcher for each time an assessment is administered
- Review participant folders to ensure the accuracy, completeness, and legibility of the data.
- Any correction made to the source documents is dated, initialed, and explained. The original entry should not be obscured.
- The protocol-specific source documents are on file.
- Source documents are completed in ink.
- Note to files (Appendix F) are made for missing or incomplete data and to explain any discrepancies or additional comments.

DNA.

- Participant names will not be on any of the samples collected. DNA is sequenced to check for one nucleotide. When testing is performed, only de-identified information is shared with an outside party. This information will not be shared with anyone outside of the study personnel, including the participant.

12.4 DATA MANAGEMENT RESPONSIBILITIES

The responsibilities designated to each member of the research team are documented on the Delegation of Authority Form. The study coordinator and research assistants will be responsible for the informed consent process, review for eligibility, questionnaire administration, data entry, device administration, and EKG administration. 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. Karen McCulloch will be the medical monitor for the study.

REDCap will serve as a secure data management tool for this study. The study coordinator and research assistants will have complete access to the REDCap system, while the PI and Co-I will have read-only ability. This will enable to researchers to enter the data and the PI and Co-I to review.

12.5 DATA CAPTURE METHODS (REDCAP)

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.

All assessments completed by the participant at home will be completed via REDCap as well, ensuring participant security and confidentiality.

12.6 PROTOCOL DEVIATIONS

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

12.7 RECORD RETENTION

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

13 ETHICAL CONSIDERATIONS

13.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with the principles set forth in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

13.2 INSTITUTIONAL REVIEW BOARD (IRB)

The Office of Human Research Ethics is responsible for ethical and regulatory oversight of research at UNC-Chapel Hill that involves human participants. The OHRE administers, supports, and guides the work of the Institutional Review Boards and all related activities. Any research involving human participants proposed by faculty, staff, or students must be reviewed and approved by an IRB before research may begin, and before related grants may be funded. OHRE and the IRBs are critical components of the coordinated Human Research Protection Program, which serves to protect the rights and welfare of human participants. All components of this program must work together to ensure institutional compliance with ethical principles and regulatory requirements. The following is a mission statement for the coordinated Human Research Protection Program:

The University of North Carolina at Chapel Hill is committed to expanding and disseminating knowledge for the benefit of the people of North Carolina and the world. An important part of that commitment to knowledge is research of the highest quality on all aspects of the health and behavior of people, and such research is only possible through the participation of humans as research participants. Human participants are partners in research and a precious resource to the university. At UNC-Chapel Hill, human participant research is a privilege, but not a right. Consistent with that philosophy, it is the mission of the UNC-Chapel Hill Human Research Protection Program to ensure that:

- a. The rights and welfare of human participants are paramount in the research process;
- b. The highest standards of ethical conduct are employed in all research involving human participants;
- c. Research investigators are properly trained in the ethical and regulatory aspects of research with human participants;
- d. Research investigators deal honestly and fairly with human participants, informing them fully of procedures to be followed, and the risks and benefits of participating in research; and
- e. Research using human participants at UNC-CH conforms to applicable local, state, and federal laws and regulations and the policies of the university.

13.3 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of tACS will be provided to the participants 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.

Together, the researcher and potential participants will review the clinical trial in its entirety by reviewing the consent form together in a private location. 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 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.

13.4 EXCLUSION OF WOMEN, MINORITIES, AND CHILDREN (SPECIAL POPULATIONS)

Non-English speaking individuals are excluded because the ability to accurately and complete communicate study information, answer questions about the study, and obtain consent is necessary. Female participants will be asked if there is any reason to believe they might be pregnant. Pregnant participants will be excluded despite the fact that theoretical risk to mother or fetus is exceedingly small, since no safety data for pregnancy is known to exist for transcranial current stimulation studies. All women of child-bearing potential will be asked to take a pregnancy test during the initial session in order to determine eligibility for the study.

13.5 PARTICIPANT CONFIDENTIALITY

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

All data will only be referenced by dummy identifier code. Data will be stored on a password protected computer. A key connecting names and code numbers will be kept in a locked cabinet, accessible only by research personnel. All data will be stored and analyzed on password protected computers, also only accessible by research personnel. Participants will not be identified in any report or publication about this study. See *10 Data Handling and Record Keeping* for more information on source documentation storage and security.

13.6 STUDY DISCONTINUATION

In the event that the study is discontinued, participants who have completed or who are still enrolled in the study will be notified. Any new information gained during the course of the study that might affect participant's willingness to continue will be communicated within 2 days of the PI learning this information.

14 PUBLICATION POLICY

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

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APPENDIX A: SCHEDULE OF EVENTS

A detailed schematic describing all visits and assessments.

	Phone Screening	First Stimulation (Sham or 10 Hz)	2 Days Later	Second Stimulation (Sham or 10 Hz)	2 Days Later
Procedures					
Provide Verbal Consent	x				
Signed Consent Form		x			
Signed HIPAA Authorization		x			
Assessment of Eligibility Criteria	x	x			
Review of Medical History	x	x			
Review of Concomitant Medications	x	x			
Baseline Assessments (list assessments)		x			
Clinical Assessments		x		x	
Pressure Pain Threshold Test		x		x	
Urine Pregnancy Test		x			
Randomization		x			
Stimulation		x		x	
Stimulation Questionnaire, Perceived Improvement Questionnaire, HAM-D		x		x	
Email Questionnaires (Follow-up)			x		x

APPENDIX B: AE REPORT FORM

Adverse Effects Report:

Reasons for Report (adverse event, time, date and place of occurrence if available):

1. What do we already know about the therapy?
 - a.
2. What is the temporal relationship of the AE to the study therapy?
 - a.
3. Does the AE improve or disappear when the therapy is stopped?
 - a.
4. Is the AE a worsening of baseline symptom(s)?
 - a.
5. Is the AE a result of an underlying concurrent medical condition(s) or concurrent medication(s)?
 - a.
6. Additional Information provided by research team
 - a.

Research team member signature _____

Date _____

Co-Investigator:

Steps to be taken (if applicable)

Co-I signature _____

_____ Date _____

PI Comments:

Steps to be taken (if applicable)

PI signature

Date

APPENDIX D: AE REPORT FORM

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

APPENDIX E: INFORMED CONSENT QUIZ

Name of Research Study:

You have been asked to be in a research study. This sheet will help you think of questions to ask but you may have other questions. This is not a test. We want to be sure you understand what it means to be in this research study. You should understand the research before you decide whether or not to participate.

1. What is the purpose of the research?
2. What are the possible benefits of the research?
3. What are the possible risks of the research?
4. Will everyone receive the same treatment?
5. How is this research different than the care or treatment I would get if I wasn't in the research study?
6. Does the research cost me anything extra?
7. Can you stop being in the research once you've started?
8. Who will view your medical records?
9. Who do you call if I have questions about being a research subject?
10. Any questions?

APPENDIX G: TELEPHONE SCRIPT

Hello, my name is _____ and I am a study coordinator from the University of North Carolina at Chapel Hill conducting a research study about individuals with chronic low back pain. Based on your medical history, you may be eligible to participate in our study.

- If participant asks “How did you get my name and contact information?”
 - **Answer:** We received IRB approval to access medical records of patients in the UNC Health Care System who meet our research study criteria. Based on your medical history, you appear eligible to participate in this study. If you are not interested in participating in this study, we will destroy all information that we have already collected about you.
- If participant states, “but I am not a UNC Health Care patient, I go to Rex Hospital.”
 - **Answer:** UNC Health Care System now includes several affiliate hospitals and clinics, include Rex.

Do you have time now to hear about the study, answer a few screening questions, and schedule your first visit?

(If ‘No’, ask for a good time to call back)

(If ‘Yes’, proceed)

Great! This study is looking at abnormal rhythms of brain activity in patients with chronic low back pain and how they respond to very weak applied electric currents. Findings from this study will help the development of treatments for the symptoms of chronic pain. In this study, a very weak electric current will be applied to your scalp. Some people report a mild tingling because of this stimulation, but no other side effects have been found. It is not a shock and should cause no pain.

Participation in this study includes two sessions, consisting 2 stimulation sessions, separated by 1-3 weeks. You will be compensated for your time spent participating in the study. The maximum compensation for this study is \$55 for completing all of the sessions. Are you still interested in participating?

(If ‘No’, thank them for their time; if ‘Yes’, proceed)

Great! In order to make sure you’re eligible for the study, I need to ask you a few questions. Please answer yes or no. You do not need to provide any further details.

(If the answer given is not the same as the answer shown, thank the individual for his or her interest and say, unfortunately, they do not qualify for the current study)

- Are you 18 years old or older? (Yes)
- Have you ever, or are you currently being treated for a neurological condition (e.g., epilepsy, migraines)? (No)
- Are you currently taking medication for the treatment of chronic pain or any other psychiatric illness?
 - Have you ever taken medication for chronic pain?
 - Have you taken ever taken opioids, benzodiazepines or anticonvulsant medications?
 - If yes, has it been at least 6 months since then?
- Have you ever had brain surgery? (No)
- Do you have any brain devices or implants, including a cochlear implant or aneurysm clip? (No)
- Have you ever been diagnosed with a traumatic brain injury?
 - If yes, how severe?
- (For females only) Is there a chance you may be pregnant? (No)

Diagnostic

CONFIDENTIAL

- Have you been diagnosed with chronic lower back pain by a professional (i.e., a physical therapist or other license clinician)?
- Have you been diagnosed with any other co-morbid pain conditions such as fibromyalgia, nerve damage, or multiple sclerosis?
- Do you have chronic pain anywhere besides your back)?
- Does your pain radiate to other parts of your body (i.e. down your leg)? (radicular pain)

Follow-up Questions

- Have you ever been hospitalized?
 - If yes, was it in anyway related to your chronic pain or another psychiatric condition?
 - If yes, when did this occur?

<p>Phone Screening:</p> <p><input type="checkbox"/> Pass</p> <p><input type="checkbox"/> Fail</p> <p>Reason for failing: _____</p> <p>_____</p> <p>_____</p> <p style="text-align: right;">Initials _____</p>
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You are eligible for participation in the first session of the study. At the first session we will determine your eligibility for the remainder of the sessions and complete some baseline assessments. I'd like to schedule your first session now. It will last approximately 2-4 hours. All testing will be conducted UNC Hospital.

<p>Scheduled Initial Session (Enter into Clinical Trials Calendar)</p> <p>Date: _____</p> <p>Time: _____</p>

I will send you an email confirming this time, and providing directions on how to find the specific location of your session. We will also send you an email to confirm your appointment 24 hours beforehand. Please respond to this email so we know you are still coming. If you have any questions before then, please don't hesitate to contact us at this phone number or at jhprim@email.unc.edu. Thank you for your time.