STILL 3

Targeting Auditory Hallucinations with Alternating Current Stimulation

NCT number NCT03221270
Document Date 06/07/2020

STILL 3
Targeting Auditory Hallucinations with Alternating Current Stimulation

Protocol Identifying Number: 17-1364

Principal Investigator: Dr. Flavio Frohlich, PhD

Co-Investigators: Dr. Fred Jarskog, MD, Dr. John Gilmore, MD

Funded by: National Institute of Mental Health (NIMH)

Draft or Version Number: v.1.5

2 May 2017

Last Updated: 7 June 2020

Table of Contents

LIST OF ABBREVIATIONS

ACT	Assertive Community Treatment
AE	Adverse Event
AHRS	Auditory Hallucination Rating Scale
ANOVA	Analysis of Variance
BACS	Brief Assessment of Cognition in Schizophrenia
BDNF	Brain Derived Neurotrophic Factor
CAPA	Corrective and Preventative Action
CFR	Code of Federal Regulations
Co-I	Co-Investigator
CRF	Case Report Form
CRMS	Clinical Research Management System
dl-PFC	Dorso-lateral Prefrontal Cortex
DMV	Department of Motor Vehicles
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (Version IV)
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EEG	Electroencephalogram
ECG	Electrocardiogram
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRV	Heart Rate Variability
HPSVQ	Hamilton Program for Schizophrenia Voices Questionnaire
Hz	Hertz
ICA	Independent Component Analysis
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IRB	Institutional Review Board
JAMA	Journal of the American Medical Association
LAR	Legally Authorized Representative
mA	Milli-amps
MRI	Magentic Resonance Imaging
NCPRC	North Carolina Psychiatric Research Center
NIBs	Non-Invasive Brain Stimulation
NIH	National Institutes of Health
NRB	Neurosciences Research Building
OHRE	Office of Human Research Ethics
OHRP	Office for Human Research Protections
PANSS	Positive and Negative Syndrome Scale
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SCID	Structured Clinical Interview for DSM-IV Axis I Disorders
sMRI	Structural Magnetic Resonance Imaging
SOP	Standard Operating Procedure
tACS	Transcranial Alternating Current Stimulation
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation

TPJ	Temporo-parietal Junction
UDS	Urine Drug Screen
UE	Unexpected Event
UNC	University of North Carolina
UNC-CH	University of North Carolina at Chapel Hill
US	United States

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by 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, and 21 CFR Part 312)
- ICH E6; 62 Federal Register 25691 (May 9, 1997)

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Participants Protection and HIPAA Training.

PROTOCOL SUMMARY

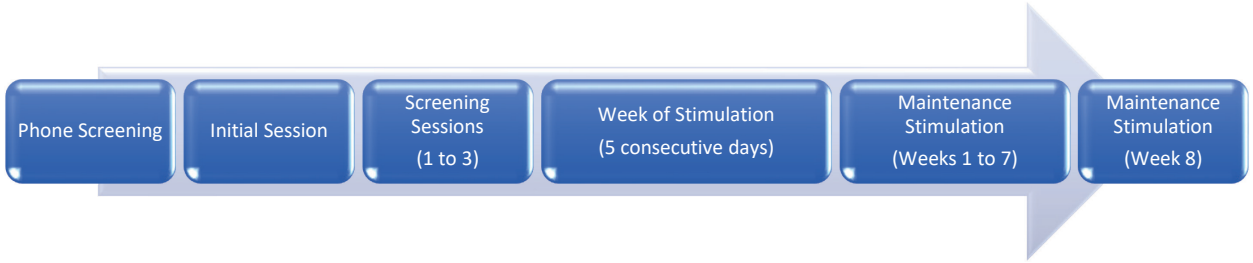
Title	STILL 3 Study
Brief Summary	The purpose is to provide further evidence concerning the efficacy of tACS for treatment of auditory hallucinations and to evaluate an exploratory maintenance stimulation paradigm to prolong the duration of stimulation-induced clinical benefits. We will study 40 eligible males and females diagnosed with schizophrenia or schizo-affective disorder. The longitudinal experimental design is a two-treatment, 4-sequence, multi-period randomized crossover design. During the first week, the enrolled participants will have 5, daily, 40-minute stimulation sessions. At the end of the first week, the participants will begin an 8-week maintenance regimen of weekly 40-minute stimulation sessions. A randomization protocol will be used to assign each participant to either a sham regimen or an active regimen during the first week, and to a sham or active maintenance regimen. Equal numbers of participants will be assigned by random allocation to the four treatment-sequence groups: tACS-tACS, tACS-sham, sham-tACS, sham-sham. Participation will involve 1 to 18 visits. At the initial phone session, informed consent will be obtained and subjects will be screened for eligibility. Participants will be contacted again in 2 weeks for a second phone screening session to determine stability of auditory hallucination symptoms, utilizing the Auditory Hallucinations Rating Scale (AHRS, attachment 3). If the AHRS scores are with ±20% of their previous score, they will be considered eligible. If the AHRS scores do not fall within this range, participants will be rescheduled for a third or fourth screening session separated by 2 weeks. If, after the fourth screening session the participant does not have stable AHRS scores, they will not be eligible to participate. Eligible participants will be scheduled for their daily stimulation sessions which will include a daily assessment of stimulation side-effects. Clinical assessments of auditory hallucinations will be administered with the AHRS and the self-administered Hamilton Program for Schizophrenia Voices (HPSVQ). These measurements will be assessed at the time of enrollment into the study (baseline), at the first day of stimulation, at the fifth day of stimulation, and once weekly for 8 weeks of maintenance stimulation sessions. Neurophysiological (EEG) and cognitive assays will be performed day 1 of stimulation, day 5 of stimulation, and at maintenance stimulation sessions for weeks 1, 3 and 8. In conjunction with

	the EEG data, we will also be collecting ECG data. An sMRI visit will be scheduled between the end of the 5th day of stimulation, and the first maintenance stimulation session.
Objectives	Our primary objective is to conduct a randomized clinical trial to investigate the ability of tACS to renormalize pathological alpha oscillations in dl-PFC of patients with schizophrenia and schizoaffective disorder and experiencing auditory hallucinations by comparing sham and active treatment regimens in terms of longitudinal changes in AHRS scores and other measures. We also aim to evaluate the ability of an 8-week maintenance regimen to prolong the duration of stimulation-induced clinical benefits in tems of longitudinal changes in AHRS scores and other measures. We hypothesize that (1) tACS reduces auditory hallucination symptoms after 5 consecutive days of daily stimulation and (2) repeat application of tACS during a follow-up maintenance regimen extends the duration of the clinical benefits of the initial stimulation. Our secondary objective is to collect further data demonstrating the value of oscillations and connectivity measures derived from EEG data as novel biomarkers in the treatment of medication refractory auditory hallucinations in schizophrenia with transcranial current stimulation. To reach this objective, we will test the working hypothesis that (1) baseline impairment in EEG oscillations and connectivity predicts treatment success, and (2) changes in these markers correlate with improvement of clinical symptom presentation as measured by the AHRS, PANSS (*Attachment 5*), and BACS *(Attachment 6).* We will collect data to support our working hypothesis by measuring whole-head EEG data with individual locations of scalp electrodes and structural MRI from all patients in our study (40 patients from Aim 1) before and immediately after the five day course of stimulation and at each maintenance stimulation visits for weeks 1, 3 and 8.
End date	December 2020
Target Population	We will recruit 40 males and non-pregnant females ages 18-70 with a diagnosis of schizophrenia or schizoaffective disorder, who have at least 3 auditory hallucinations per week, with no change in medication dosing for at least 4 weeks, not currently taking any benzodiazepine medication, and have been clinically stable for at least 12 weeks, with no change in their level of care during that period. Participants will be recruited from the Chapel Hill, Durham and Raleigh areas.
Phase	Preliminary Study
Number of Sites	This is a single site study performed at University of North Carolina - Chapel Hill.
Study Agent	We will be using an active sham and 10 Hz tACS. Active sham treatment will include 10 seconds of ramp in to 20 seconds of 10 Hz tACS with a ramp out of 10 seconds for a total of 40 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 also have a 10 second ramp in and ramp out with 40-minutes of stimulation for a total of 1220 seconds during the week of stimulation. During the maintenance week sessions, stimulation sessions will be a one session for a total of 40-minutes. Stimulation waveforms are sine-waves with a peak-to-peak amplitude of 2 mA.

Study Duration	This study will take 30 months to complete
Participant Duration	Eligible participants who complete this clinical trial will have a total of 15 to 18 visits; an initial session, 1 to 3 follow up screening sessions, 5 consecutive days of daily stimulation,1 MRI scan session, and 8 once weekly maintenance stimulation sessions. Maintenance sessions will begin the week after the 5 days of stimulation have been completed. The initial screening session will take approximately 2 hours, each follow up screening session will last approximately 30 minutes, and the first day of stimulation will take approximately 4 hours. Days 2 through 4 of stimulation will take 1.5 hours each day. Day 5 of stimulation will last about 4 hours. The sMRI visit will last no longer than 2 hours. Maintenance stimulation sessions weeks 1 and 3 will take approximately 3 hours. Maintenance sessions weeks 2, 4, 5, 6, and 7 will take approximately 2 hours. Maintenance session week 8 will take approximately 5 hours. We estimate that total participation to be approximately 35-39 hours.

SCHEMATIC OF STUDY DESIGN

At enrollment, the 40 eligible enrollees will be allocated by randomization to four treatment-sequence groups: tACS-tACS, tACS-sham, sham-sham, sham-tACS) (10 participants per sequence). The randomization will be stratified by sex.



1 KEY ROLES

Individuals:	**Principal Investigator:** Flavio Frohlich, Ph.D.
	Co-Investigator: Fred Jarskog M.D., John Gilmore, M.D
	Flavio Frohlich Ph.D. – Principal Investigator UNC - Chapel Hill Department of Psychiatry Email: flavio_frohlich@med.unc.edu Office: 4109 Neuroscience Research Building Phone: (919) 966-4584 Fred Jarskog M.D- Co-Investigator UNC - Chapel Hill Department of Psychiatry Email: lars_jarskog@med.unc.edu Office: Medical School Wing D, Rm 254 Phone: (919) 843-7683

	John Gilmore M.D- Co-Investigator UNC - Chapel Hill Department of Psychiatry Email: john_gilmore@med.unc.edu Office: 304 MacNider Hall Phone: (919) 445-0209 Rachel Force, Ph.D. – Clinical Trials Director UNC-Chapel Hill Department of Psychiatry Email: *Rachel_force@med.unc.edu* Office: Medical School Wing C-233 Phone: (919)966-9929
Institutions:	University of North Carolina- Chapel Hill
Other:	IRB University of North Carolina-Chapel Hill 720 Martin Luther King Jr. Blvd Bldg#385, Second Floor CB #7097 Chapel Hill, NC 27599-7097 (919) 966-3113 National Institute of Mental Health Sponsored Programs Office, SOM 1140-C Bioinformatics Bldg., CB9525 Chapel Hill, NC 27599-9525

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

About, 30% of patients with schizophrenia have auditory hallucinations that are refractory to antipsychotic medication and cause a significant decrease in quality of life (Shergill, Murray et al. 1998). All effective antipsychotics introduced over the past 60 years have been premised on dopamine D2 receptor antagonism, but clearly this mechanistic approach does not help all patients. For this reason, novel treatment approaches are required and transcranial current stimulation represents once such promising approach. Thus far, attempts at using transcranial current stimulation for treating medication refractory auditory hallucinations in patients with schizophrenia have been limited to the use of tDCS (Brunelin, Mondino et al. 2012). However, tDCS does not specifically target the known deficits in neuronal synchronization (alpha frequency band functional connection) between the cortical areas that may play a causal role in auditory hallucinations (Winterer, Coppola et al. 2003).

Patients with schizophrenia exhibit disorganized neuronal network dynamics such as hypoactivity in the dorso-lateral prefrontal cortex (dl-PFC) and hyperactivity in the temporo-parietal junction (TPJ) (Silbersweig, Stern et al. 1995; Lawrie, Buechel et al. 2002). A recent provocative study has suggested that these abnormalities can be targeted by transcranial direct current stimulation (tDCS) (Brunelin, Mondino et al. 2012) resulting in a significant decrease in auditory hallucinations that outlasts stimulation for at least three months. However, the relative importance of the choices of stimulation parameters (stimulation waveform, number of treatments, treatment

schedule) remains unknown. In particular, tDCS does not target the known deficits in the temporal structure of cortical network activity in patients with schizophrenia.

2.2 RATIONALE

Here, we propose a new innovative approach driven by rational design where we use non-invasive brain stimulation to directly target the circuit-level pathology of auditory hallucinations. Specifically, we will evaluate simultaneous tACS (10 Hz) to enhance synchronization between frontal and temporo-parietal areas of the left hemisphere. Such use of tACS to enhance synchronization has recently been introduced as a successful modulator of long-range synchrony mediating working memory (Polania, Nitsche et al. 2012). Additionally, we will use EEG data to develop a novel biomarker to show that decreases in auditory hallucinations are predicted by an increase in effective and functional connectivity between key brain regions. In the EEG analysis, we will also employ source localization techniques to estimate the spatiotemporal dynamics of neuronal currents in the brain. In this step, we can minimize estimation errors of the locations and strengths of the current sources in the brain by measuring individual locations of scalp electrodes and using structural magnetic resonance imaging (sMRI). Because the source localization techniques can be problematic, small errors in a source modeling step can lead to larger errors in brain activity analysis. Anatomical brain structure and electrode location for each participant is are necessary components to get reliable and precise current sources in the brain. Ultimately, our goal is to treat patients based on demonstrable changes in brain activity, rather than on symptoms themselves. The proposed research is innovative because it employs a new form of non-invasive brain stimulation, tACS, which targets underlying functional neuropathology to treat medication refractory auditory hallucinations in schizophrenia. Additionally, we are developing novel EEG biomarkers as markers for treatment response. We recently completed a pilot clinical trial examining the efficacy of tACS compared to tDCS and sham for treating auditory hallucinations in patients with schizophrenia or schizoaffective disorder. Results from this study were negative with a strong placebo effect, however we found that tACS and sham showed lasting significant improvement of auditory hallucinations vs tDCS. Data collected in this study will be used to further understand the effect of tACS on auditory hallucinations and sustaining effects with maintenance sessions weekly for 2 months after the initial 5 days of stimulation.

2.3 POTENTIAL RISKS AND BENEFITS

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 clinical population recruited for this study may be subjected to negative consequences caused by the stigma of mental disorders. Furthermore, some might not agree with the principle of participating in research or of changing natural brain activity. To avoid breaches in confidentiality, study documents that contain personal information, including the informed consent document, and the document that links study ID numbers to personal identifying information are kept in locked filing cabinets in a locked room, 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.

Risk of Embarrassment: Self-reports and some assessments contain questions regarding sensitive personal information. This risk is necessary in order to assess experiences such as auditory hallucinations and disease state. Participants will be assured upon intake that only study personnel will see any clinical ratings, and study raters are trained to inquire about potentially distressing symptoms using a sensitive and respectful approach. Participants will be given the option not to answer questions that are too distressing.

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 mode has NOTHING to do with electroconvulsive therapy that applies many orders of magnitude higher stimulation current. Rather, transcranial current stimulation is so weak that it does not cause super-threshold activation of neurons (Frohlich and McCormick, 2010). 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 *(Attachments 1 &2)* after each stimulation session to document 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.

While not previously reported with tDCS or tACS in humans, there is a theoretical possibility that stimulation of neuronal circuits could lead to epileptic discharges. 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, the subject will be referred to a neurology clinic for further evaluation and treatment.

We have no evidence that our treatment paradigms will increase auditory hallucinations if not treated (receive the sham treatment), as participants, will be by definition, stable. If an enrolled patient shows signs of increase symptoms that were not apparent during enrollment, a referral to UNC Psychiatry will be made. Dr. Jarskog, Co-I, will facilitate this process.

MR Scanning: Magnetic resonance scanning does not involve the use of ionizing radiation. There are no known risks from MR imaging. The FDA has categorized MRI up to 8.0 Tesla as not a significant health risk. The 3T MR scanner which we will use in this study is FDA approved and all new sequences possess the same safeguards as standard (FDA approved) clinical sequences to prevent harm to subjects. On very rare occasions, the individual may feel some eye discomfort. The scanning will be stopped if this occurs. These symptoms, if present, will subside shortly after leaving the magnet. In rare occasions the subject may experience claustrophobia. If this is the case, the scan will be discontinued immediately. In rare occasions subject may experience a localized twitching sensation due to the magnetic field changes during the scan. This is not unexpected and should not be painful. However, the subject can decide to stop the imaging session at any time if this occurs. Dizziness and nausea are also rare, and more often occur when the subject is moved quickly near the magnet or if the head is moved within the bore of the magnet. If the subject deems this sensation uncomfortable, the study will be terminated.

2.3.2 KNOWN POTENTIAL BENEFITS

Our novel protocol targets the evidence for abnormal neuronal activity displayed in schizophrenia, with the intent to decrease auditory hallucinations. tACS has the promise to become the next generation stimulation

paradigm for non-invasive treatment of pathological cortical network dynamics in patients with schizophrenia. A significant benefit to society would be the ability to treat medication resistant symptoms of schizophrenia.

This study has not been designed to benefit the individual participants. The study has been designed to gain knowledge about the potential efficacy of tACS in treating auditory hallucinations in people with schizophrenia. In the event that tACS is effective, participants in this study who are randomized to the tACS arm could experience improvement in auditory hallucinations. There are no known serious risks to the participant from the interventions used in this study. The chance to understand and develop a new treatment for persistent hallucinations in schizophrenia is an important step in helping the millions of people in the world who suffer from this condition.

3 OBJECTIVES AND SPECIFIC AIMS

Our primary objective is to conduct a clinical trial to provide further evidence for evaluation of the efficacy of tACS for treatment of auditory hallucinations in patients with schizophrenia or schizoaffective disorder and explore the possible benefits of a maintenance regimen of 8 weekly sessions for prolonging symptom improvement. As a secondary objective we will evaluate treatment effects on PANSS scores and BACS scores, and assess the differential clinical effects of sham and 10 Hz on EEG measures of alpha oscillations.

Aim 1. Evaluate the relative efficacy of the tACS treatment regimen and subsequent maintenance regimen in terms of changes in the mean level of the AHRS score

Aim 2. Evaluate the relative efficacy of the tACS treatment regimen and subsequent maintenance regimen in terms of changes in the mean levels of the PANSS score and the BACS score

Aim 3. Evaluate the effects of the tACS treatment regimen and subsequent maintenance regimen in terms of changes in EEG alpha frequency power levels.

4 STUDY DESIGN AND OUTCOME MEASURES

4.1 STUDY OUTCOME MEASURES

4.1.1 PRIMARY OUTCOME MEASURES

The Auditory Hallucination Rating Scale (AHRS) will be the primary outcome measure for this study. This survey instrument will be administered at the first recruitment visit, two weeks later at the screening visit, at baseline (t_0) on the first day of stimulation, after stimulation on the fifth day of stimulation (t_1), and at each of the 8 weekly maintenance sessions (t_2, t_3,. t_4, t_5, t_6, t_7, t_8, t_9). The primary analyses will focus on longitudinal changes from baseline in the AHRS scores at t_1 and t_9 accounting for the following explanatory variables: treatment regimen, treatment stage (initial daily stimulation vs maintenance weekly stimulation), and the baseline AHRS score as a covariate.

4.1.2 SECONDARY OUTCOME MEASURES

We will compare alpha oscillations from resting state EEG recording from the first day (t_0) and last day (t_1) of the stimulation week. We will also collect EEG data at the maintenance sessions at weeks 1, 3, and 8 (t_2, t_4, t_9). We will use these data to analyze alpha frequency activity for derivation of EEG biomarkers. Furthermore, we will estimate

the locations and strengths of the current sources in the brain using source localization techniques based on individual locations of scalp electrodes and anatomical structures.

The Positive and Negative Syndrome Scale (PANSS) and Brief Assessment of Cognition in Schizophrenia (BACS) will also be secondary outcome measures for this study. These measurements will be taken at the first day of stimulation (t_0), last day (t_1) of stimulation and at the final maintenance stimulation visit (t_9). PANSS and BACS scores serve as measures of other positive, negative and general symptoms of schizophrenia (PANSS) or cognition (BACS). The analyses of these secondary measures will focus on longitudinal changes from baseline in the scores at t_1 and t_9 accounting for treatment regimen, treatment stage(initial daily stimulation vs maintenance weekly stimulation), and the baseline AHRS score as a covariate.

4.2 STUDY DESIGN

This longitudinal, single-center, randomized, sham-controlled, double-blind clinical trial will be used to collect preliminary efficacy data for use in further refinement of the tACS approach. The experimental design is a randomized, two-treatment, multi-period, 4-sequence crossover design. The 40 enrolled participants will be allocated by a randomization protocol to for treatment-sequence groups: tACS-tACS, tACS-sham, sham-sham, sham-tACS.

The target population from which we are sampling is a clinical population. We are seeking 40 males and females ages 18-70 with a diagnosis of schizophrenia or schizoaffective disorder, who have at least 3 auditory hallucinations per week, with no change in medication dosing for at least 4 weeks, not currently taking benzodiazepines or anticonvulsant medications, and have been clinically stable for at least 12 weeks, meaning no change in the level of their care. The enrolled participants will be outpatients; most will be referred through psychiatrists in the UNC Department of Psychiatry and affiliated ACT clinics, or by mental health practitioners in the local community. We estimate 30 months to complete study enrollment.

Pregnancy is an exclusion criterion. All women of child-bearing potential will have a pregnancy test at the beginning of the first day of stimulation to determine eligibility for the study. A pregnancy test will also be administered prior to the sMRI scan. Pregnancy test will also be administered to female participants of child-bearing potential at each of the weekly maintenance sessions. For post-menopausal female participants, we will administer a pregnancy test every 4 weeks at the beginning of the maintenance session in order to reduce participant burden. We will rely on self-report from female participants to determine whether they are post-menopausal by confirming that they have gone 12 months without menstruation.

Sham treatment will include 10 seconds of ramp in to 20 seconds of 10 Hz tACS with a ramp out of 10 seconds for a total of 40 seconds of stimulation. The rationale for this choice of an active sham is that it may 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 1220 seconds of stimulation, daily for five days. Stimulation waveform is a sine-wave with a peak-to-peak amplitude of 2 mA. In each treatment regimen, participants will stay in a relaxed and controlled state by watching a nature movie such as “ReefScape” during stimulation. The maintenance regimen will provide one 40-minute stimulation per week.

Eligible participants who complete this clinical trial will have a total of 15 to 18 visits; an initial screening session, a 2nd screening session, (if needed) 2 more follow up screening sessions, 5 days of daily stimulation sessions, 1 smRI visit, and 8 weekly maintenance stimulation sessions. The initial phone screening session will take approximately 2 hours, and each follow up screening session will take approximately 30 minutes each. The first day of stimulation will take approximately 4 hours and days 2 through 4 of stimulation will take 1.5 hours each. The last day of stimulation will take about 4 hours. sMRI visits will last approximately 2 hours. Maintenance stimulation sessions weeks 1 and 3 will be approximately 3 hours each, maintenance weeks 2, 4, 5, 6, and 7 will be approximately 2 hours each, and the final maintenance stimulation session week 8 will be approximately 5 hours. We estimate that total participant participation duration will be approximately 35 to 39 hours. A small subset of participants will be recruited for a 12 week observational case study to assess the feasibility of long-term at-home maintenance treatment.

In order to ensure symptom stability for each potential participant, there will be up to a 6 week period for the participant to achieve a stable AHRS score. The AHRS will be performed at 2 week intervals during screening. A stable score is defined as having less than or equal to 20% change. If the change between the first and second AHRS scores is less than or equal to 20%, then the participant will move on to the week of stimulation. If a stable score is not achieved at the second screening session, the participant will have two more opportunities at 2 week intervals during follow-up screening sessions to achieve a stable score. The participant will be paid for each session. If the participant does not achieve a stable score (if there remains a greater than 20% change in scores between consecutive AHRS administrations) by the end of the 6 weeks, the participant will not be eligible to continue participation.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

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

- DSM-IV diagnosis of schizophrenia, any subtype, or schizoaffective disorder, with refractory auditory hallucinations. Duration of illness >1 year.
- 18 – 70 years old
- Clinically stable for at least 12 weeks i.e. not requiring hospitalization or a change in level of care.
- On current antipsychotic doses for at least 4 weeks
- Experience at last 3 auditory hallucinations per week
- Stable auditory hallucinations as demonstrated by having less than or equal to 20% change in AHRS scores across a 2 week interval during the screening period
- Capacity to understand all relevant risks and potential benefits of the study and to provide written informed consent, OR has a legal guardian who can provide informed consent on the patient's behalf with the patient providing written assent to participate

5.2 PARTICIPANT EXCLUSION CRITERIA

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

- DSM-IV diagnosis of alcohol or 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 3 months
- Positive urine test of cannabis, cocaine, amphetamine, barbiturates, opiates
- Current treatment (within 4 weeks) with psychotropic agents including benzodiazepines that are taken on a daily basis (limit prn use to greater than 48 hours before participating in study session)
- Medical or neurological illness (unstable cardiac disease, AIDS, malignancy, liver or renal impairment) or treatment for a medical disorder that could interfere with study participation
- History of traumatic brain injury that required subsequent cognitive rehabilitation, or cause cognitive sequelae
- A difference greater than 20% in AHRS scores between the 3rd and 4th screening visits
- Prior brain surgery
- Any brain devices/implants, including cochlear implants and aneurysm clips
- Co-morbid neurological condition (e.g. seizure disorder, brain tumor)
- Non English speakers
- Female participants who are pregnant, nursing, or unwilling to use an adequate method of contraception during study participation for those of child bearing potential
- Anything that, in the opinion of the investigator, would place the participant at increased risk or preclude the participant's likelihood of completing all components of the study

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

We intend to recruit 40 patients with schizophrenia or schizoaffective disorder and persistent auditory hallucinations, despite optimized antipsychotic medication treatment for at least 1 month. We will do this through both the UNC Hospital as well as the NCPRC Raleigh outpatient site, in coordination with providers at both locations. Additionally, we will also be contacting local ACT teams to recruit patients as well as potentially a small number from other community mental health providers. We estimate that approximately 15 subjects will be enrolled at the UNC-CH location, approximately 15 subjects will be enrolled at the Raleigh site, and approximately 10 subjects will be enrolled through ACT teams, for a total of 40 participants. Providers will be informed of the inclusion and exclusion criteria and will be asked to discuss the study with their patients at their next appointment or home visit in the case of the ACT team. Providers will include the medical teams treating patients at either of the two locations (Chapel Hill or Raleigh). Providers will identify patients they believe to be appropriate for this study based on the information we will provide them about the study. Providers will ask patients whether they are willing to be contacted by the research team regarding participation. Providers will be asked to avoid unnecessary medication changes leading up to and over the course of the study.

Our retention strategy includes monetary compensation for the time and effort required to participate in the study. The participant will receive a payment at each session of the study. The research staff will also give each participant a reminder call for the initial screening session, each follow up screening session, the first day of stimulation, and each maintenance 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 verify 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 a professional relationship with the participants so they feel comfortable and willing to discuss what may be sensitive information. Retention will be quantified by participant attendance at each scheduled session (the data from each session will be scored and documented the day of the session). Participants will no longer be eligible to continue the study if they miss 2 consecutive stimulation sessions during the initial week of stimulation, if they miss 2 consecutive weeks of stimulation during the maintenance sessions, or if they miss more than 2 non-consecutive sessions during the course of the study. While we will ask each participant to complete an sMRI visit, it is not necessary for this visit to occur. If the participant does not want to complete the sMRI visit, the participant will be eligible to continue the remainder of the study.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

A study participant will be discontinued from further participation if:

- The participant has missed more than 2 non-consecutive stimulation sessions
- The participant has missed 2 consecutive stimulation sessions during the initial week of stimulation
- The participant has missed 2 consecutive weeks of stimulation during the maintenance sessions
- 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

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

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-specified safety 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 or Co-I.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be prematurely terminated if, in the opinion of the investigator, there is sufficient reasonable cause. Circumstances that may warrant termination include, but are not limited to:

- Discovery of unexpected, significant, or unacceptable risk to participants.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Plans to modify, suspend or discontinue the development of the study device.

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

6 STUDY INVESTIGATIONAL PRODUCT

6.1 STUDY PRODUCT DESCRIPTION

6.1.1 DEVICE DESCRIPTION

Participants will be stimulated with the commercial, CE-certified Neuroconn Plus stimulator.The use of this device in this study has previously received a NSR designation on initial review by the full UNC IRB. The NeuroConn device description is as follows:

The DC-STIMULATOR is a CE-certified medical device for conducting non-invasive transcranial direct-current stimulation (tDCS) in humans. DC stimulation is used in clinical practice and in the research of stroke, epilepsy, migraine, tinnitus, depression, multiple sclerosis, dementia and chronic headache. The DC-STIMULATOR is a micro-processor-controlled constant current source. It meets the highest safety standards thanks to (hardware- and software-based) multistage monitoring of the current path. By continuously monitoring electrode impedance it can detect insufficient contact with the skin and automatically terminate stimulation, maximizing patient safety.

The device's alphanumeric display and the 4 touch keys allow various stimulation modes to be selected and stimulation parameters such as current strength, duration, fade-in and fade-out to be set.

DC-STIMULATOR features:

- 1 channel (anodal and cathodal stimulation possible)
- Adjustable current up to 5,000 µA *
- Adjustable application time up to 30 minutes *
- 2 standard modes - single (continuous stimulation) and - pulse (cyclical stimulation activation/deactivation) with fade in and fade out
- Customer-specific programs possible (optional)
- "Study mode" for blind processing of genuine and 'pseudo' stimulation (optional)
- External trigger input (optional)

6.1.2 OPERATION

A. The desired current value is scaled to a register value and stored in the function generator.

B. The value in the register determines the percent of full scale output current, generated by the function generator.

C. The generated current waveform from the function generator is driven through a specified resistance. The resulting voltage drop is amplified by an instrumentation amplifier.

D. The voltage waveform from the output of the instrumentation amplifier is applied to a voltage controlled current source.

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 generates 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 overcurrent 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 sensor output is then shifted before it is read by the microprocessor using the same level shifting circuit described in the current sensor section.

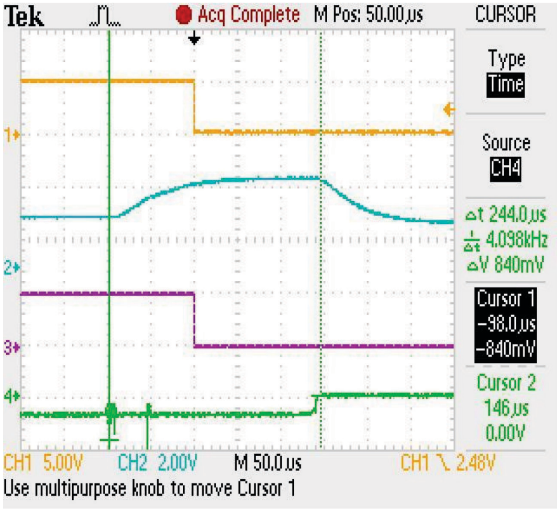
6.1.3 SAFETY PRECAUTIONS

The device is equipped with 4 different stages of safety protection, all of which protect the stimulant 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 +/-3mA 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 +/-4.5mA. 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 successful hardware cutoff function



3. Permanent hardware current cutoff. A 5mA 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 stimulant will no longer be electrically connected to the device.

4. Power supply fuse. Finally, if for any 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.

Digitizing scanner

We will be using a GeoScan digitizing scanner to scan individual locations of scalp EEG electrodes. The GeoScan handheld digitizing scanner integrates into OEM neurodiagnostic equipment to measure, identify, and map electrode positions (via attached markers). This is based on optical 3D measurement technology that scans up to 256 markers in less than 2 minutes to accuracy within 0.5 mm and repeatability of 0.1 mm. Real-time compensation for data variability ensures only actual markers are measured for mapping and registration purposes.

GeoScan Digitizing Scanner

- Features

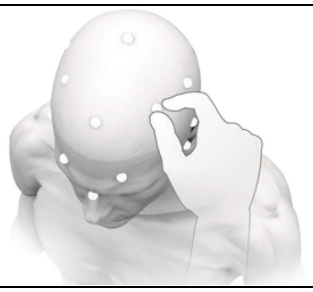
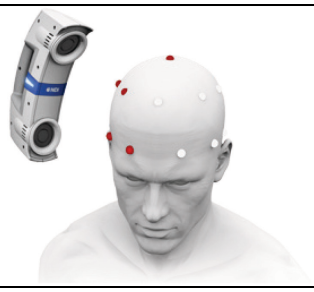
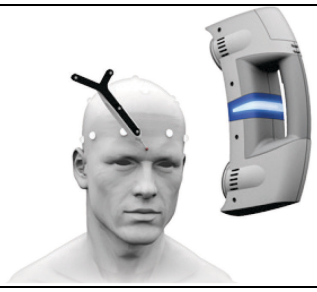
Scanner Specifications

Dimensions (LxWxH)	155 mm x 75 mm x 300 mm
Weight	860 g
Power Requirements	100-250 V AC ~50/60 Hz, 1 A

Sensor Specifications

Measurement Volume	883 mm x 840 mm x 928 mm
Update Frequency	20, 30, 60 Hz
Scan Rate	256 markers < 2 minutes
Accuracy	Within 0.5 mm RMS
Stand-off	105 mm from the scanner
Depth of View	778 mm
Near field width	276 mm
Far field width	840 mm
Safety	IEC 60601-1 3rd Edition

- Operation

		
1. Attach each electrode (with prefixed marker) to the scalp or cap.	2. Scan the head with the device to localize each marker's position. This localization process creates a digital point cloud (3D model) and rigid body of marker coordinates.	3. Probe anatomical features to establish fiducial (reference) points with respect to the rigid body, such as the nasion, inion, and preauricular points of the subject's head.

7 STUDY PROCEDURES/EVALUATIONS

7.1 STUDY SPECIFIC PROCEDURES

During the initial session, researchers will collect demographics. Participant demographics include medical history and medication history. This information is used to confirm inclusion criteria and that no current alcohol and drug abuses or disorder exist.

Several clinical evaluations will be used throughout this study. These assessments are listed below and can be found in the attached documents.

i. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) is a semi-structured interview used to diagnosis major Axis I disorders. For this study, the SCID-I (First et al. 2004) will be administered at baseline in order to confirm a diagnosis of Schizophrenia or Schizoaffective Disorder.

ii. The Columbia Suicide Severity Rating Scale (C-SSRS) is a semi-structured interview designed to assess suicidality. The assessment will be administered at baseline, the first day of stimulation, the fourth maintenance stimulation session, and the final maintenance stimulation session.

iii. The Auditory Hallucination Rating Scale (AHRS) is a structured interview, designed to assess different aspects of patient's auditory hallucinations. This assessment has 11 items and is rated on a scale of 0 – 4 based on the responses given by the patient. The AHRS will be administered at the baseline visit, each screening session, the first day of stimulation, the last day of stimulation, and at each of the maintenance stimulation sessions.

iv. The Positive and Negative Syndrome Scale (PANSS) is a structured interview used to assess the symptom severity of patients diagnosed with schizophrenia. The PANSS (Kay et al. 1987) focuses on the positive and negative syndromes and their general severity. This scale will be administered at the

first day of stimulation, the last day of stimulation and at the final maintenance stimulation session (week 8).

v. The Brief Assessment of Cognition in Schizophrenia (BACS) will be administered at the first day of stimulation, the last day of stimulation and at the final maintenance stimulation session (week 8) in order to monitor changes in participant cognition. This validated assessment (Keefe et al. 2004, Keefe et al. 2006) contains 6 tests that focus on verbal memory and learning, working memory, motor functioning, attention/processing speed, verbal fluency and reasoning and problem solving.

7.2 STANDARD OF CARE STUDY PROCEDURES

We will be monitoring the safety of our participants throughout the study with the following assessments. These assessments can also be found in attachments.

i. 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. A similar questionnaire was used in IRB #13-2995, #14-3285, and #14-1622 to evaluate ability to successfully blind using transcranial current stimulation. *(Attachment 1 and Attachment 2)*.

7.3 LABORATORY PROCEDURES/EVALUATIONS

7.3.1 CLINICAL LABORATORY EVALUATIONS

During the initial session, all participants will be asked to participate in a urine drug screen in order to help screen out any individuals who have a drug use problem. A urine pregnancy test will also be performed at the beginning of the first day of stimulation for any female participant who is of child-bearing potential. A urine pregnancy test will also be performed prior to the sMRI scan, and at each maintenance sessions for women of child-bearing potential.

7.3.2 OTHER ASSAYS OR PROCEDURES

The Brief Assessment of Cognition in Schizophrenia (BACS) *(Attachment 6)* will be administered during the 1st day of stimulation, the 5th day of stimulation and at the final maintenance stimulation session (week 8). This assay was specifically designed to assess cognition in patients diagnosed with schizophrenia and will be used to obtain a baseline assessment of cognition in each participant. We will also be using this assay as a safety monitor and data collection tool throughout the study to assess any changes in cognition that may be seen as a result of the treatment.

There will be two procedures used throughout this study. Each participant will attend 5 consecutive weekdays of stimulation for this study. Each participant will be randomly assigned to one of four treatment-sequence groups for this study (sham or 10HZ tACS). Electrodes with a measurement of 5x5cm will be placed between Fp1 and F3 and between T3 and P3, and a return electrode, 5x7cm, will be placed over Cz. In order to detect any change(s) at the neurophysiological level, an EEG will be performed during the 1st day of stimulation, the 5th day of stimulation, and at each of the maintenance stimulation sessions. This measurement will contribute to the design of novel network-level biomarkers of schizophrenia and of treatment response. In the EEG analysis, we will employ source localization techniques to estimate the spatiotemporal dynamics of the neuronal currents in the brain. In order to reduce prediction errors and get more reliable and precise prediction, we will collect individual locations of EEG

electrodes using a digitizer(GeoScan) and structural MRI (sMRI) for each participant that is willing/able to safely complete an sMRI scan. These two additional information can help to make a well-constructed head model and source model for reconstructing location and the time-course or spectral content of a source in the brain. The electrode localization scanning using the GeoScan will be applied at each EEG recording, as there is the possibility for slight changes in electrode location at each EEG net application. As the structure of the brain will not change over the course of participation, the electrode localization for each EEG recording will be applied to the sMRI image to make the head model.

During each EEG recording, we will also be collecting ECG data. These ECG electrodes will be a part of the EEG acquisition system and will be placed on the participant's body, ideally one electrode below the right collarbone and a second one below the chest on the left. This data will be collected to look at HRV across conditions.

7.4 STUDY SCHEDULE

7.4.1 SCREENING

Screening Telephone Call
Individuals who are referred by a mental health care provider will be contacted by a researcher for an initial phone screening. Researchers will keep a Telephone Contact log for each telephone conversation with a participant throughout the study. There will be a log for each participant.

During the telephone screening, researchers will provide a brief background about Schizophrenia and tACS. Any initial questions will be answered at this point. The timeline of visits will then be explained; there will be 1 to 18 sessions, with 1 initial session, anywhere from 1 to 3 follow up screening sessions, 5 consecutive week days of daily stimulation, 1 MRI scan session, and maintenance stimulation sessions once weekly for 2 months following the initial 5 days of stimulation. The participant will be informed that compensation for their participation will be received at each session throughout the study. The participant will be asked if they have any additional questions. Once all questions have been answered, the participant will be asked if he/she is still interesting in participating in the study. If yes, the researcher will begin the initial phone screening which will determine eligibility for the initial session. The screening questions are shown below. If the required answers are given for each question, the initial session will be scheduled and a reminder call will be given at least 24 hours before initial session. We will use the approved telephone script for all telephone screenings.

7.4.2 ENROLLMENT/BASELINE

Initial Screening Visit (Visit 1, Day 0)
At the consent visit, participants will go over the consent form mailed to their address and all questions will be answered before they document their consent through a REDCap eConsent form. Each form will be read to the participant by the researcher, and the participant will be given the time to ask any questions about the information discussed. Each participant will be asked a series of questions (*Appendix E*) to ensure that the consent form is fully understood. Participants will physically sign both a HIPAA authorization form and the consent form to be mailed back to the researcher or brought to the first lab visit. The researcher will verify that the participant meets inclusion criteria. Next, the SCID (*Attachment 4*) will be administered in order to confirm diagnosis of schizophrenia or schizoaffective disorder and to verify that the participant does not have active alcohol or illicit drug abuse or dependency. The participant will be asked to provide verbal consent to record their SCID interview. They may

decline the recording and continue in the study. The C-SSRS (screening version) will be administered next. If a participant answers 'yes' to items 3, 4, or 5 in the suicidal ideation section in the past month or answers 'yes' to any suicidal behavior within the past six months, the study coordinator will call Dr. Jarskog, who will determine if an acute assessment is needed. Dr. Jarskog will conduct this acute assessment if it is needed. Once the diagnosis has been confirmed, a baseline Auditory Hallucinations Rating Scale (AHRS) will be administered to document hallucinatory severity and frequency. Demographic information will be collected, which will include a history of medication, alcohol, and drug use. A short handedness questionnaire, a Belief about Treatments questionnaire, the BIS/BAS scale, and the HPSVQ will also be self administered via REDCap survey. The 2nd screening visit will be scheduled for approximately 2 weeks later. The participant's payment will be placed in an envelope to be mailed after the screenings are completed or distributed at the first lab visit.

2nd Screening Visit (Visit 2)

The 2nd screening visit will also take place over webex. The following questionnaires will then be administered to further check eligibility; Auditory Hallucination Rating Scale (AHRS) in order to document any change in auditory hallucination severity/frequency (*Attachment 3*). The AHRS scores from the initial screening visit and the current visit will be compared. If a change in score greater than 20% exists, then a 3rd screening visit will be scheduled for approximately 2 weeks later. If a change in AHRS score is less than or equal to 20% and eligibility has been confirmed, the week of stimulation will be scheduled. The participant's payment will be placed in the original envelope to be mailed after the screenings are completed or distributed at the first lab visit.

3rd Screening Visit (Possible Visit 3)

The 3rd screening visit will also take place over webex. The following questionnaires will then be administered to further check eligibility; Auditory Hallucination Rating Scale (AHRS) in order to document any change in auditory hallucination severity/frequency (*Attachment 3*). The AHRS scores from the 2nd screening visit and the current visit will be compared. If a change in score greater than 20% exists, then a 4th screening visit will be scheduled for approximately 2 weeks later. If a change in AHRS score is less than or equal to 20% and eligibility has been confirmed, the week of stimulation will be scheduled. The participant's payment will be placed in the original envelope to be mailed after the screenings are completed or distributed at the first lab visit.

4th Screening Visit (Possible Visit 4)

The 4th screening visit will also take place over webex. The following questionnaires will then be administered to further check eligibility; Auditory Hallucination Rating Scale (AHRS) in order to document any change in auditory hallucination severity/frequency (*Attachment 3*). The AHRS scores from the 2nd screening visit and the current visit will be compared. If a change in score greater than 20% exists, then the participant is considered not eligible to participate and will be paid for completing the session. If a change in AHRS score is less than or equal to 20% and eligibility has been confirmed, the week of stimulation will be scheduled. If the participant is considered not eligible to participate, their payment will be placed in the original envelope to be mailed. If they are eligible the payment will be added to the original envelope to be distributed at the first lab visit.

7.4.3 STIMULATION WEEK

Day 1 of Stimulation (Visit 5)

Upon participant arrival, a completed consent form and HIPAA authorization will be confirmed to be in the participant file. All participants (male and female) will be asked to complete a urine drug screening to determine eligibility for the study. Female participants will complete a urine pregnancy test to rule-out pregnancy. Vital signs

will be taken. The C-SSRS (screening version) will be administered next. If a participant answers 'yes' to items 3, 4, or 5 in the suicidal ideation section or answers 'yes' to any suicidal behavior since the initial screening visit, the study coordinator will call Dr. Jarskog, who will determine if an acute assessment is needed. Dr. Jarskog will conduct this acute assessment if it is needed. Then, the AHRS (*Attachment 3*) will be administered followed by the PANSS (*Attachment 5*) and the Brief Assessment of Cognition in Schizophrenia (BACS) *(Attachment 6)*. The BACS will be used as a baseline assessment of participant cognition, and will be administered again during later sessions to assess for any changes in cognitive function associated with treatment. An EEG will then be administered, with ECG data also being collected at this time. The EEG recording will include resting state data along with an auditory task, and the EEG Questionnaire will be administered.

Once the questionnaires are complete, the participant will be administered either sham or 10 Hz tACS treatment for 40-minutes. Participants will be asked to sit still and not talk during these 40-minutes, and will be asked to keep their eyes open and facing straight ahead. The *Reefscape* video will be played during the stimulation session. After each stimulation treatment, to assess any side effects of stimulation, the stimulation adverse effects questionnaire will be administered. This questionnaire will be administered at the end of each stimulation session as a safety assessment to monitor any potential side effects of the stimulation (*Attachment 1*). Participants will be paid for this visit as well as all previous screenings at the conclusion of this session.

Days 2 – 4 of Stimulation (Visit 6 – 8)
Upon participant arrival, vital signs will be taken. The participant will then receive 40-minutes of sham or 10 Hz tACS (as per the initial randomization) while sitting quietly with their eyes open. The *Reefscape* video will be played during each stimulation session. Each stimulation session will be followed by the stimulation adverse effects questionnaire. Participants will be paid at the conclusion of each session.

Day 5 of Stimulation (Visit 9)
The participant will be asked to decide if they would like to complete the clinical assessments over the phone or in person. If they prefer the phone/webex, the participant will be contacted before coming into the lab and the AHRS (*Attachment 3*) and PANSS (*Attachment 5*) will be administered. Upon participant arrival at the lab, vital signs will be taken and documented at the beginning of the first stimulation session of the day. An EEG will then be administered, with ECG data also being collected at this time. The EEG recording will include resting state data along with an auditory task, and the EEG Questionnaire will be administered. The participant will receive 40-minutes of sham or 10 Hz tACS (as per the initial randomization) while sitting quietly with their eyes open. The *Reefscape* video will be played during the stimulation session. Each stimulation session will be followed by the stimulation adverse effects questionnaire. The BACS *(Attachment 6)* data collection assessments will be administered at the end of this session. If the participant opted to complete the clinical assessments in person, the AHRS (*Attachment 3*) and the PANSS (*Attachment 5*) will be administered at the end of this session. After the assessments are completed, the participant will then be paid at the completion of the session, and the first maintenance session will be scheduled for the second week after their last day of stimulation (one gap week in between).

7.4.4 STRUCTURAL MRI VISIT

sMRI Scan Visit (Visit 10)

During the gap week between the 5th day of stimulation and the 1st maintenance session, we will ask the participant to come in and complete an sMRI scan. MRI scan imaging will take place at the Biomedical Research

Imaging Center (BRIC), located in Marsico Hall on the first floor. If the participant is a female of child-bearing potential, they will be asked to complete a urine pregnancy test prior to completing the scan. Screening questions asked prior to the MRI scan (*Attachment 8*) and all preparation for scans will take place in a facility area behind a locked door, where only research study personnel have access. When subjects are required to change their clothing, they will be allowed to do so alone, in a room with a door that locks. MRI scan will be performed by trained study personnel or designees of the PI that are approved to complete an MRI scan.

7.4.5 MAINTENANCE SESSIONS

Maintenance Stimulation Session Week 1 (Visit 11)
Upon participant arrival, vital signs will be taken and documented. Female participants will complete a urine pregnancy test to rule-out pregnancy. An EEG will then be administered, with ECG data also being collected at this time. The EEG recording will include resting state data along with an auditory task, and the EEG Questionnaire will be administered. The participant will receive 40-minutes of sham or 10 Hz tACS (as per the randomization) while sitting quietly with their eyes open. The stimulation session will be followed by the stimulation adverse effects questionnaire. The AHRS and HPSVQ will then be administered to assess severity of auditory hallucinations. Participants will be paid at the conclusion of this study visit, and the next study visit will be scheduled for the following week.

Maintenance Stimulation Session Week 2 (Visit 12)
Upon participant arrival, vital signs will be taken and documented. Female participants will complete a urine pregnancy test to rule-out pregnancy. An EEG will then be administered, with ECG data also being collected at this time. The EEG recording will include resting state data along with an auditory task, and the EEG Questionnaire will be administered. The participant will receive 40-minutes of sham or 10 Hz tACS (as per the randomization) while sitting quietly with their eyes open. The stimulation session will be followed by the stimulation adverse effects questionnaire. The AHRS and HPSVQ will then be administered to assess severity of auditory hallucinations. Participants will be paid at the conclusion of this study visit, and the next study visit will be scheduled for the following week.

Maintenance Stimulation Session Week 3 (Visit 13)
Upon participant arrival, vital signs will be taken and documented. Female participants will complete a urine pregnancy test to rule-out pregnancy. The C-SSRS (follow-up version) will be administered next. If a participant answers 'yes' to items 3, 4, or 5 in the suicidal ideation section or answers 'yes' to any suicidal behavior since the week of stimulation, the study coordinator will call Dr. Jarskog, who will determine if an acute assessment is needed. Dr. Jarskog will conduct this acute assessment if it is needed. An EEG will then be administered, with ECG data also being collected at this time. The EEG recording will include resting state data along with an auditory task, and the EEG Questionnaire will be administered. The participant will receive 40-minutes of sham or 10 Hz tACS (as per the randomization) while sitting quietly with their eyes open. The stimulation session will be followed by the stimulation adverse effects questionnaire. The AHRS and HPSVQ will then be administered to assess severity of auditory hallucinations. Participants will be paid at the conclusion of this study visit, and the next study visit will be scheduled for the following week.

Maintenance Stimulation Session Week 4-7 (Visits 14-17)
Upon participant arrival, vital signs will be taken and documented. Female participants will complete a urine pregnancy test to rule-out pregnancy. The participant will receive 40-minutes of sham or 10 Hz tACS (as per the randomization) while sitting quietly with their eyes open. The stimulation session will be followed by the

stimulation adverse effects questionnaire. The AHRS and HPSVQ will then be administered to assess severity of auditory hallucinations. Participants will be paid at the conclusion of this study visit, and the next study visit will be scheduled for the following week.

7.4.6 FINAL STUDY VISIT

Maintenance Stimulation Visit Week 8 (Visit 18)

Upon participant arrival, vital signs will be taken and documented. Female participants will complete a urine pregnancy test to rule-out pregnancy. The C-SSRS (follow-up version) will be administered next. If a participant answers 'yes' to items 3, 4, or 5 in the suicidal ideation section or answers 'yes' to any suicidal behavior since the third week of maintenance, the study coordinator will call Dr. Jarskog, who will determine if an acute assessment is needed. Dr. Jarskog will conduct this acute assessment if it is needed. An EEG will then be administered, with ECG data also being collected at this time. The EEG recording will include resting state data along with two auditory tasks, and the EEG Questionnaire will be administered. The participant will receive 40-minutes of sham or 10 Hz tACS (as per the randomization) while sitting quietly with their eyes open. After the session participants will complete the stimulation adverse effects questionnaire. The AHRS and HPSVQ will be administered to assess severity of auditory hallucinations, followed by the adverse events questionnaire and a review of current medications. The PANSS (*Attachment 5*), and BACS *(Attachment 6)* data collection assessments will be administered at the end of this session for endpoint assessment. Each participant will be asked whether they believe their symptoms have changed (better, worse, no change) over the course of the study. After the assessments are completed, the participant will then be paid for the completion of the final study visit.

7.4.7 CASE STUDY

Case Study

A subset of participants (up to 4) will be recruited from the original participant pool for a 12-week case study evaluating the feasibility of long-term maintenance. Participants will self-identify as being interested, and the PI and CO-Is will then determine eligibility. Participants will receive 40-minutes of 10Hz tACS while sitting quietly with their eyes open, once per week for 12 weeks. Each stimulation will be followed by the stimulation adverse effects questionnaire and the AHRS and HPSVQ to assess severity of auditory hallucinations. Participants will not receive monetary compensation for the case study.

7.4.8 SCHEDULE OF EVENTS TABLE

Procedures	Initial Visit via webex	Screening Visit (2-4) via webex	Day 1 of Stimulation	Days 2-4 of Stimulation	Day 5 of Stimulation	sMRI Visit	Maintenance Stimulation (Week 1)	Maintenance Stimulation (Week 2)	Maintenance Stimulation (Week 3)	Maintenance Stimulation (Weeks 4 – 7)	Maintenance Stimulation (Week 8)
eConsent REDCap	X										
Signed Consent Form			X								
SCID	X										
C-SSRS	X		X						X		X
Demographics	X										
Med History	X										
Medications	X----------										----------X
Handedness	X										
Beliefs about Tx	X										
BAS/BIS	X										
AHRS	X	X	X		X		X----------				----------X
HPSVQ	X	X	X		X		X----------				----------X
Vital Signs			X----------		----------X		X----------				----------X
Pregnancy test			X			X	X----------				----------X
Urine Drug Screen			X								
PANSS			X		X						X
BACS			X		X						X
Randomization			X				X				
Stimulation			X	X	X		X----------				----------X
EEG			X		X		X		X		X
EEG Questionnaire			X		X		X		X		X
AE Interview			X----------		----------X		X----------				----------X
Sx improvement Q's					X		X----------				----------X
sMRI						X					
HRV			X		X		X		X		X

7.5 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

We have included maintenance sessions in the study schedule in order to examine lasting effects of tACS. After the final maintenance session, no further treatment will be offered.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

There will be three different assessments used to ensure participant safety. First, vitals will be recorded at the beginning of each session. This assessment is used to monitor any physiological changes.

A Positive and Negative Syndrome Scale will be administered before the first stimulation session and on the last day of stimulation as well as at the one month follow up. This tool is used to assess any changes in symptoms associated with this disorder. We do not expect any changes in these symptoms; additionally we did not find any changes in related clinical trials (IRB# 13-2995, IRB #14-3285). Should there be a significant change in PANSS rating scores, (>25% increase) we will direct the participant to Dr. Jarskog for further follow up and file a AE report.

The Columbia Suicide Severity Rating Scale will be administered at the initial session and roughly monthly intervals thereafter. The tool is used to assess recent and lifetime suicidality and will primarily determine if Dr. Jarskog should be called to conduct an acute assessment. Should a participant answer "yes" to items 3,4, or 5 on the Suicidal Ideation section or "yes" to any Suicidal Behavior question within a recent time period (specified above), Dr. Jarskog will be called to conduct an acute assessment and we will file an AE report.

After each stimulation session, a stimulation adverse effects questionnaire (*Attachment 1and Attachment 2)* will be administered. This tool is used to document any side effects experienced during stimulation. The researcher will also check with the participant throughout the 20 minute stimulation sessions to make certain no discomfort is felt. The stimulation session will be terminated if the participant reports having unmanageable discomfort or pain (more than "moderate"). Additionally, this information will be reported on an AE report form *(Appendix A)* and an AE log *(Appendix B)*.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse Event: An AE, as defined by the NIH, is any unfavorable changes in health, including /abnormal laboratory findings that occur in trial participants during the clinical trial or within a specified period following the trial.

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 Interview will be completed by the study coordinator during each lab visit (see attachment*).* For any Adverse events reported, a clinician will evaluate and indicate the severity of the event(s). The AE report form (*Appendix A)* will be completed for any reported AE. The AE form includes the following: what is known about the therapy and 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 a worsening of baseline symptoms or related to a concurrent medical condition or medication use. Once complete, both of these forms will be given to the PI and the Co-I who will review, comment and sign the forms. Completed forms will be placed in the participant's folder.

The study coordinator will document any AE occurrence on the AE log (*Appendix B)* which includes information such as the date of the AE, severity, relationship to the treatment (assessed by the PI), actions taken, and outcome(s). The log will be reviewed and initialed 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 the study treatment. Any medical condition noted at the initial session will be considered as 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 the event; no treatment needed.
- **Mild** Adverse Event– 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** Adverse Event – 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 adverse event the medical advisor may recommend an over the counter medication.
- **Severe and undesirable** Adverse Event – Event results in significant symptoms that prevents 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 G)* and will be filed in the participant's folder.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

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 C)*, 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 binder 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 has been notified, and the date that the SAE Form was completed.

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unexpected Events (UE) will be recorded on the UE/SAE log (*Appendix D)* and will include information including date of the event, when the study team was informed of this event, event details, 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 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.

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.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

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

- **Asymptomatic:** the participant is exhibiting no symptoms due to the event; no treatment needed.
- **Mild AE**– 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 AE** – 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 adverse event the medical advisor may recommend an over the counter medication.
- **Severe and undesirable AE** – Event results in significant symptoms that prevents 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 G)* and will be filed in the participant's folder.

8.2.2 RELATIONSHIP TO STUDY AGENT

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 the 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.

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

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

8.4 REPORTING PROCEDURES

We will be adopting the following procedures 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	Within **24 hours** of initial receipt of information	Investigator	• Local/internal IRBs, DSMB

serious adverse reactions			
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 Problems	Within **30 days** of the IRB's receipt of the report of the UP from the investigator.	IRB	• OHRP
		Investigator[3]	• External IRBs

8.4.1 REPORTING OF PREGNANCY

Pregnancy tests will be administered at the beginning of the first day of stimulation and at each of the maintenance sessions to all women of child-bearing potential. A pregnancy test will also be administered prior to the sMRI scan 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/ medical monitor.

8.5 STUDY HALTING RULES

If a seizure or any other Grade III adverse event 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 it is found after investigation that the seizure was not related to the stimulation then the temporary hold of the study will be lifted. If, after investigation into the seizure or Grade III adverse event occurs, and there is found to be further well tested and documented safety measures that can be employed in the study to prevent further seizures or Grade III adverse events, then the temporary hold on the study will be lifted. 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 and previous studies in the lab using tACS (IRB14-1622, IRB14-3285) have had no seizures occur (Berlin et al., 2013, Brunelin et al., 2012). The study will also be stopped if other studies provide evidence that transcranial current stimulation has been associated with other, previously unrecognized, potentially harmful effects, either short-term or long-term.

8.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a DSMB composed of Dr. Ross Simpson, an epidemiologist, a biostatistician and one or more clinical researchers. The DSMB will review AEs every 6 months whereas the medical monitor will review AEs in real time and make decisions as to each participant's continuation in the trial.

The PI will review AEs weekly with research team and may request additional review by Co-I on a case-by-case basis. The medical monitor will also be present at weekly meetings in order to discuss/explain any event(s) that may occur.

Every 6 months DSMB will review blinded AE reports. If there is reason to view unblinded information, the DSMB will directly receive the list of participants' identification numbers from a Frohlich Lab member, not otherwise associated with this clinical trial. Participant identification number will be displayed in a table according to the four treatment-sequence groups of the study; however the specific treatment regimens of the four groups will not be disclosed. This will allow the DSMB to compare the four treatment groups.

Reasons for stopping the study and asking for further investigation include; decrease in cognitive abilities based on baseline and end of study data (>25% decrease in scores in 2/10 of the first participants or 20% of participants overall.). In addition, as mentioned above, if a seizure occurs during a study visit, the clinical trial will be temporarily be placed on hold for further investigation.

9 CLINICAL MONITORING

The Purpose of the monitoring plan is to present the Frohlich Lab'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.

Frohlich Lab 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 (*Appendix H*) 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 at the Clinical Trials desk in Rm 233 of the Medical School Wing C. Deviations will be sent to IRB every 4-6 weeks (if necessary).

The PI will always be available by phone or email to the study coordinator or research assistant in the case of an adverse event. The study coordinator or research assistant will keep the PI up to date on all occurrences throughout the study's continuation in a timely manner, making sure the PI is aware of any events as soon as possible.

AE and SAE are clearly defined in the Master Protocol. Documents of AE and SAE can be found in the study binder on file at the Clinical Trials desk in Rm 4109 of the NRB. It is responsibility of the study coordinator to report all events to the PI. For our practices we have adapted the decision tree provided by UNC-CH IRB to assist with reporting of such events (*Attachment 7*). The PI will have read-only access to the redcap data base for this study. At any time the PI can check and make sure that data entry is complete and accurate for each participant. This

allows the PI 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 STATISTICAL CONSIDERATIONS

10.1 STUDY HYPOTHESES

We hypothesize that

(1) Daily tACS stimulation for 5 days reduces auditory hallucination symptoms as measured by the AHRS, PANSS and BACS survey instruments, and that

(2) weekly tACS stimulation during a follow-up maintenance regimen extends the duration of that clinical benefits as measured by the AHRS, PANSS and BACS.

We hypothesize that

(1) baseline impairment in EEG oscillations and connectivity predicts treatment success, and that

(2) changes in these markers are correlated with improvement of clinical symptom presentation as measured by the AHRS, PANSS, and BACS.

10.2 STATISTICAL ANALYSIS PLANS

The following statistical considerations and aim-specific analysis plans will be reviewed and updated prior to any data collection. To help ensure reproducibility and objectivity of the results, these *a priori* plans specify details for the main analyses for each specific aim; e.g., details of fitted models and decisions regarding the units and scales of the measurements of interest. The plans include 1) sensitivity analyses performed to assess the robustness of the major results to reasonable perturbations of the assumptions and methods used; 2) exploratory analyses for hypothesis generation; 3) necessary descriptive graphical and tabular methods used to visualize the data, and 4) exploration of relationships among the variables of interest. Following best practices (e.g., www.CONSORT-statement.org), all statistical estimates (e.g., variances, means, differences) will be reported along with their 95% confidence intervals (C.I.s). Hypothesis tests that are observed to be not statistically significant will be reported as being inconclusive. (Hypothesis tests that are not statistically significant are entirely inconclusive and no conclusions can be drawn from those tests. Statistical test procedures are incapable of establishing that the null hypothesis is true.) The word "inconclusive" will be used when reporting a test that was not statistically significant. To avoid over-reliance on p-values, the focus of the analyses will be on the point-estimates and interval-estimates of the magnitudes of the population parameters of interest (e.g. treatment effects).

Plans for Aim 1: *Evaluate the relative efficacy of the tACS treatment regimen and subsequent maintenance regimen in terms of changes in the mean level of the AHRS score.*

Clinical scores (AHRS, PANS, BACS) will be recorded on nine occasions (t): at baseline immediately before the first stimulation session on day 1 (t_0), after the stimulation session ending day 5 (t_1), and after each weekly maintenance session (t_2, t_3, t_4, t_5, t_6, t_7, t_8, t_9). The experimental design is best viewed as a 2-treatment, 4-sequence (SS, SA, AS, AA), 2-period randomized crossover with longitudinally repeated measures during the second period. Equivalently, it can also be viewed as a 2-treatment, 4-sequence, 9-period crossover.

For AHRS, $Y_{ij}(t_0)$ is the baseline score from the i-th participant in the j-th treatment sequence (j = SS, SA, AS, AA). The primary analyses will focus a linear mixed-effects model for the change from baseline on occasion t, $\Delta Y_{ij}(t) = Y_{ij}(t) - Y_{ij}(t_0)$, conditional on the following explanatory variables: assigned treatment regimen, treatment stage (initial daily stimulation vs maintenance weekly stimulation), and baseline score $Y_{ij}(t_0)$ as a covariate.

$$[\, \Delta Y_{ij}(t) \mid \underline{X}\,,\, Y_{ij}(t_0)\,] = \mu_S X_1 + \mu_A X_2 + \tau_S X_3 + \tau_A X_4 + \lambda X_5 + \beta\,(Y_{ij}(t_0) - \bar{Y}(t_0)) + \varepsilon_i + \varepsilon_{ij}(t)$$

Here, $\bar{Y}(t_0)$ is the average of all baseline values. The expected value is shown in **Table 1** below. The fitted model will be used to tabulate statistical estimates (all with 95% confidence intervals) of the population parameters of interest: variance components, intra-class correlation, the direct effect of treatment ($\mu_S - \mu_A$) in period 1, treatment-specific period effects (τ_A, τ_S), and a longer-term treatment effect (λ) that carries over from period 1 into period 2. Parameters τ_A and τ_S represent both the period-by-treatment interaction and also the 'period effect' ($\tau_A + \tau_S$). In a 2-sequence crossover design, parameters τ_A, τ_S and λ would be aliased together; whereas, in the 4-sequence design they are not aliased. For the main analysis we assume carryover effect λ vanishes in the later weeks of the maintenance regimen in period 2; that is, effects of any treatments in period 1 have washed out by the end of the maintenance regimen. (That would not be the case if treatment A in period 1 cured the patient.) The sensitivity of the main results to this assumption will be investigated in auxiliary sensitivity analyses. In this model, the direct treatment effect in period 1 is ($\mu_S - \mu_A$) while the direct treatment effect in period 2 is $((\mu_S + \tau_S) - (\mu_A + \tau_A))$. We conjecture that $\tau_S \approx 0$ and that τ_A has a small negative value owing to weekly stimulation having a somewhat smaller effect than daily stimulation. The magnitude of τ_S is of interest because it represents the efficacy of montly stimulation relative to daily stimulation. The magnitude of λ is of interest because it represents impact of treatment that endures into (at least) the beginning of the maintenance regimen.

Table 1. Conditional expected value of change from baseline evaluated at the average baseline value

		Treatment Sequence			
		SS	SA	AS	AA
Period 1	t_1	m_S	m_S	m_A	m_A
Period 2	t_2	$m_S + t_S$	$m_A + t_A$	$m_S + t_S + l$	$m_A + t_A + l$
	t_3	$m_S + t_S$	$m_A + t_A$	$m_S + t_S + l$	$m_A + t_A + l$
	t_4	$m_S + t_S$	$m_A + t_A$	$m_S + t_S + l$	$m_A + t_A + l$
	t_5	$m_S + t_S$	$m_A + t_A$	$m_S + t_S + l$	$m_A + t_A + l$
	t_6	$m_S + t_S$	$m_A + t_A$	$m_S + t_S$	$m_A + t_A$
	t_7	$m_S + t_S$	$m_A + t_A$	$m_S + t_S$	$m_A + t_A$
	t_8	$m_S + t_S$	$m_A + t_A$	$m_S + t_S$	$m_A + t_A$
	t_9	$m_S + t_S$	$m_A + t_A$	$m_S + t_S$	$m_A + t_A$

For the primary analysis, the above model will be fitted using only AHRS scores at $t \in \{ t_1, t_9 \}$ assuming λ=0:

$$E[\, \Delta Y_{ij}(t) \mid \underline{X}\,,\, Y_{ij}(t_0)\,] = \mu_S X_1 + \mu_A X_2 + \tau_S X_3 + \tau_A X_4 + \beta\,(Y_{ij}(t_0) - \bar{Y}(t_0))$$

The set of sensitivity analyses will include fitting the model using AHRS scores at $t \in \{ t_1, t_6, t_7, t_8, t_9 \}$ (with λ=0), which is anticipated to provide more precision and power for analysis of the treatment effects.

The analyses will focus on the point estimates and confidence interval estimates of the parameters of interest; for example, $(\mu_S - \mu_A)$ and $((\mu_S + \tau_S) - (\mu_A + \tau_A))$. The data and the fitted model will be visualized via graphical figures. The fitted model using only AHRS scores at $t \in \{t_1, t_9\}$ will be used to test the primary null hypothesis, H_o: "$(\mu_S - \mu_A) = 0$ and $(\tau_S - \tau_A) = 0$", using an F-test of size $\alpha = 0.05$.

To explore carryover of treatment effects, the model

$$E[\Delta Y_{ij}(t) \mid \underline{X}, Y_{ij}(t_0)] = \mu_S X_1 + \mu_A X_2 + \tau_S X_3 + \tau_A X_4 + \lambda X_5 + \beta (Y_{ij}(t_0) - \bar{Y}(t_0))$$

will be fitted using AHRS scores recorded on occasions $t \in \{t_1, t_2, t_3, t_4, t_5, t_6, t_7, t_8, t_9\}$.

Sensitivity analyses will be used to evaluate the robustness of the main results to reasonable perturbations of the methods and assumptions used. This set of analyses will examine goodness of fit diagnostics for the linear model, and will include modified versions of the main analyses.

Plans for Aim 2. *Evaluate the relative efficacy of the tACS treatment regimen and subsequent maintenance regimen in terms of changes in the mean levels of the PANSS score and the BACS score.*

We anticipate that the strategy and methods used for the analyses of AHRS scores in Aim 1 will also be appropriate for the analysis of PANSS and BACS scores for Aim 2.

Plans for Aim 3. *Evaluate the effects of the tACS treatment regimen and subsequent maintenance regimen in terms of changes in EEG alpha frequency power levels*.

We anticipate that the strategy and methods used for the analyses for Aim 1 will also be appropriate for the analyses in Aim 3 of changes in alpha band power calculated from EEG recordings. Graphical descriptive statistical methods will be used to visualize and summarize the temporal trajectories of the scores and alpha band power. Scores of clinical assessments and EEG recordings at other occasions of the maintenance sessions may be explored for the purpose of generating hypotheses.

Plans for early discontinuation: In the event of a participant discontinuing participation prior to completion of the study sessions, the participant's data set will not be included in analysis. Only completed data sets will be included in analysis.

10.3 SAMPLE SIZE CONSIDERATIONS

It is difficult to recruit a large number of patients diagnosed with schizophrenia with persistent auditory hallucinations to participate in a single site extensive study. However, based on our recent experience recruiting for patients with these symptoms, we expect that we can successfully recruit 40 subjects from this population.

We evaluated the performance characteristics of the study design and analysis strategy under the assumption that only 40 subjects will be available. To do this we used information from a previous randomized study conducted in this lab (IRB 14-3285). That study obtained baseline AHRS scores (Y_0) and post-treatment AHRS scores (Y_1) from participants sampled from our target population using the same methods and inclusion/exclusion criteria. **Table 2** lists information obtained: 7 patients received sham treatment (***S***), 8 received 10Hz tACS treatment (***A***).

Table 2. Parameter Estimates from Previous Study

Parameters in Target Population	Estimate	95% C.I. Lower	Upper	N
Means				
E[Y1 - Y0 | S]	**-2.29**	-4.27	0.31	**7**
E[Y1 - Y0 | A]	**-3.75**	-6.15	-1.35	**8**
Serial Correlation				
Corr[Y1, Y0 | S]	0.93	0.60	0.99	7
Corr[Y1, Y0 | A]	0.91	0.56	0.98	8
Corr[Y1, Y0 | S and A] = ρ	*0.90**			
Variance Components				
Var [Y1 - Y0 | S]	**4.58**	1.90	22.21	**7**
Var [Y1 - Y0 | A]	**8.24**	3.60	34.12	**8**
Var [Y1 - Y0 | S and A] = $\sigma^2_{difference}$	5.82	3.11	14.45	15**
Var [Y1] = V[Y0] = $\sigma^2 = \sigma^2_{difference} / 2(1 - \rho)$	29.10	15.57	72.23	
Var [Y1 - Y0 | Y0] = $\sigma^2_{conditional} = \sigma^2 (1 - \rho^2)$	5.53	2.96	13.72	
Inter-subject component of $\sigma^2_{conditional}$	4.98	2.66	12.35	
Intra-subject component of $\sigma^2_{conditional}$	0.55	0.30	1.37	
Standard Deviations (square-root of variance)				
SD [Y1 - Y0 | S]	**2.87**	1.38	4.71	**7**
SD [Y1 - Y0 | A]	**2.14**	1.90	5.84	**8**
SD[Y1 - Y0 | S and A] = $\sigma_{difference}$	2.41	1.76	3.80	15**
SD[Y1] = SD[Y0] = σ	5.39	3.95	8.50	
SD[Y1 - Y0 | Y0] = $\sigma_{conditional}$	2.35	1.72	3.70	
Inter-subject component of $\sigma_{conditional}$	2.23	1.63	3.51	
Intra-subject component of $\sigma_{conditional}$	0.74	0.54	1.17	

* We conjecture that ρ is near 0.90 in the target population mindful that it is plausible that ρ could be as small as 0.56 or as large as 0.99. Here, 0.90 is not a statistical estimate; it is a conjecture based on the tabulated estimates.

** The variance estimate is a pooled estimated. We conjecture that the variance components have the same magnitudes for treatments S and A.

For purposes of our analysis of anticipated precision and power, we conjectured that 1) the variance components have the same magnitudes for treatments S and A, and 2) the magnitude of intra-class correlation is 0.90. The tabulated correlation estimates suggest that the post-treatment AHRS score is highly correlated with the AHRS score at baseline (t_0). Consequently it is desirable to use the baseline score as a covariate in the linear mixed-effects model for AHRS change-from-baseline in order to improve precision and power for the analysis of treatment effects.

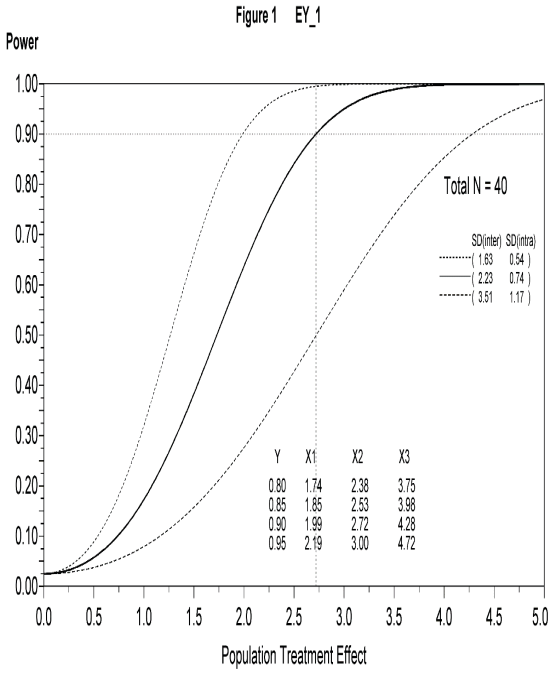
Based on **Table 2** estimates for AHRS, we anticipate that 20 participants per regimen in period 1 will provide a margin of error of about 1.0 AHRS unit for regimen-specific estimates of mean change from baseline; i.e., we anticipate a 95% C.I. of the form [mean change $\pm$ 1.0] for each regimen.

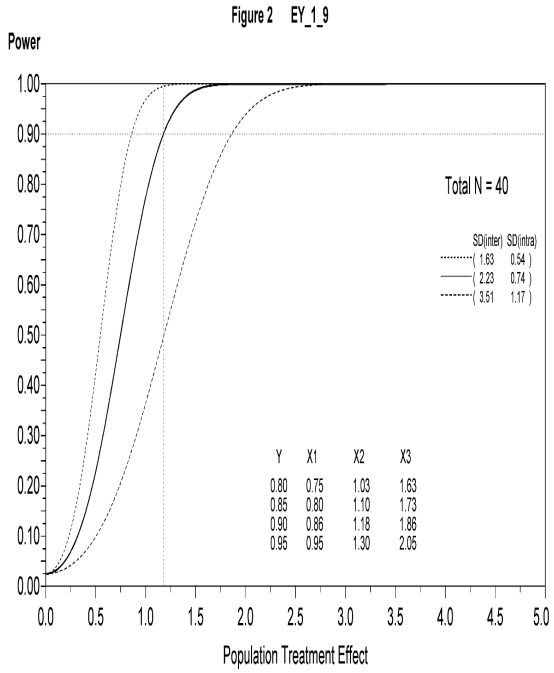
For the primary analysis, the model will be fitted using only AHRS scores at $t \in \{ t_1 , t_9 \}$:

$$E[\Delta Y_{ij}(t) \mid \underline{X} , Y_{ij}(t_0)] = \mu_S X_1 + \mu_A X_2 + \tau_S X_3 + \tau_A X_4 + \beta (Y_{ij}(t_0) - \bar{Y}(t_0))$$

We will test H_o: "$(\mu_S - \mu_A) = 0$ and $(\tau_S - \tau_A) = 0$", using an F-test of size $\alpha = 0.05$. However, for purposes of the analysis of anticipated power, we considered a close surrogate: testing H_o: "$(\mu_S - \mu_A) = 0$" and H_o: "$(\tau_S - \tau_A) = 0$" separately using F-tests each of size $\alpha = 0.025$. In **Figure 2**, power curves are for the test of H_o: "$(\mu_S - \mu_A) = 0$".

The curves are based on the point-estimates and 95% C.I. estimates of intra-subject and inter-subject variance components expressed here as standard deviations (by taking square roots) which are in turn based on the data in Table 2 and based on a conjectured underlying correlation of 0.90 between t_0 and t_1.





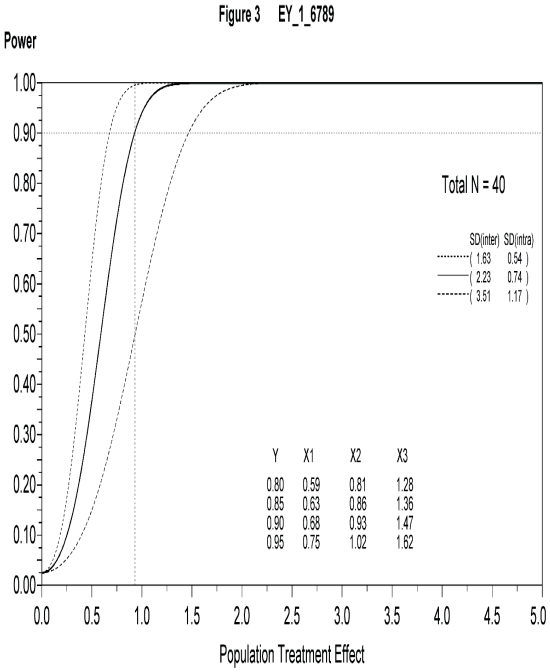
The probability ('power') of drawing a sample that yields a p-value < α = 0.025 is a function of the unknown magnitude of the treatment effect ($\mu_S - \mu_A$) in the target population. In **Figure** 2, for example, if our conjectures and assumptions are true and in truth ($\mu_S - \mu_A$) = 1.18 AHRS units, the likelihood of rejecting H_o:"($\mu_S - \mu_A$)=0" is estimated to be 90% with C.I. [50%, 99%]. For comparison, **Figure 1** provides power curves for a test of H_o:"($\mu_S - \mu_A$)=0" based on only the data from period 1 --an approach that does not take advantage of the crossover design.

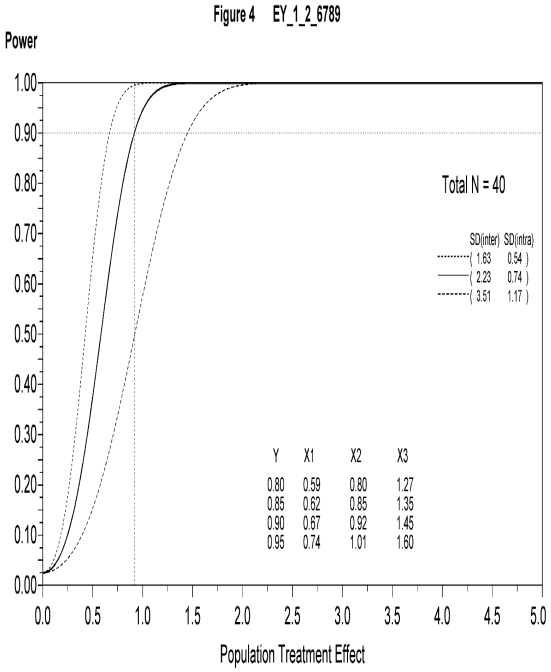
Figure 3 provides similar information for test of H_o: "($\mu_S - \mu_A$) = 0" based on AHRS scores recorded on occasions $t \in \{ t_1, t_6, t_7, t_8, t_9 \}$ assuming carryover effect λ has vanished before t_6. Inclusion of the carryover effect in the model can reduce precision and power for the test of treatment effects.

When exploring carryover effects using scores from occasions $t \in \{ t_1, t_2, t_6, t_7, t_8, t_9 \}$ to fit

$$E[\, \Delta Y_{ij}(t) \mid \underline{X}, Y_{ij}(t_0) \,] = \mu_S X_1 + \mu_A X_2 + \tau_S X_3 + \tau_A X_4 + \lambda X_5 + \beta\, (Y_{ij}(t_0) - \bar{Y}(t_0)),$$

the power curves in **Figure 4** indicate anticipated power levels for a test of H_o: "($\mu_S - \mu_A$) = 0" when it is assumed that carryover impacts the score at t_2 but not the scores at t_6, t_7, t_8 and t_9.





It is anticipated that some participants will have incomplete data. **Figures 5, 6, 7 and 8** indicate the performance of the test procedures when the sample size is reduced to 30 participants. (Compare to Figures 1, 2, 3 and 4).

Figures 1 - 8 were computed using the ability of SAS PROC MIXED to calculate the non-centrality parameter of the distribution of the F-statistic for a competely specified linear mixed-effects model. The resulting power-curve estimates are conjectures based on 1) previous data from only 15 subjects, 2) assumptions about the appropriate model for the data, 3) an assumption that the variance components have the same magnitudes for treatments S and A, and 4) an assumption that the correlation coefficient for the model's compound-symmetry covariance structure is 0.90.

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

The follow-up case study will be used to assess feasibility of long-term maintenance. The sample size is low as we do not intend to perform statistical analysis on outcomes. This observational study will be used to inform future, large-scale studies evaluating treatment efficacy of this intervention.

Figure 5 EY_1

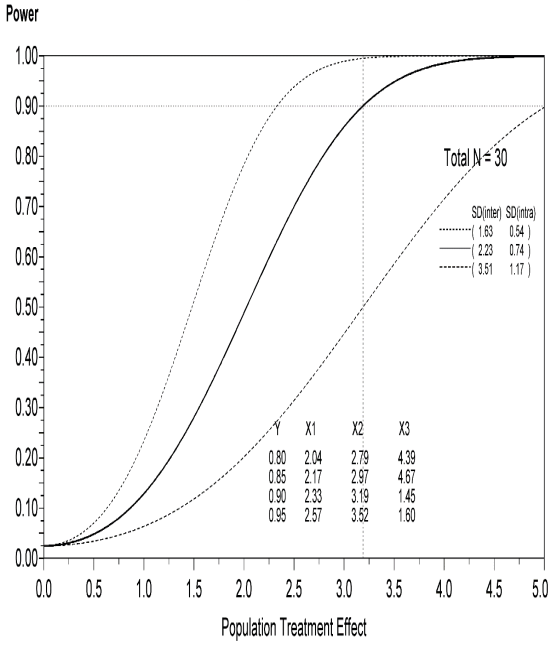


Figure 6 EY_1_9

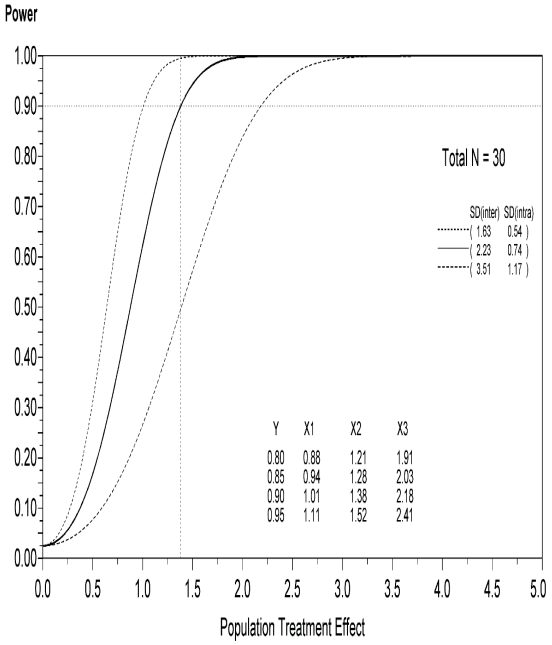


Figure 7 EY_1_6789

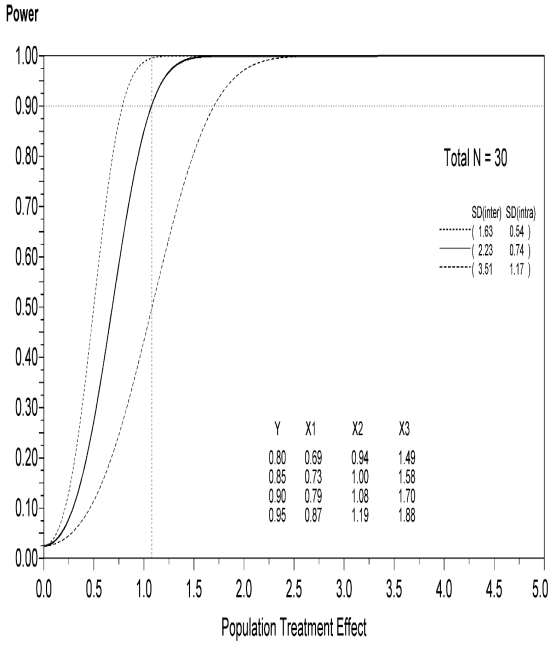
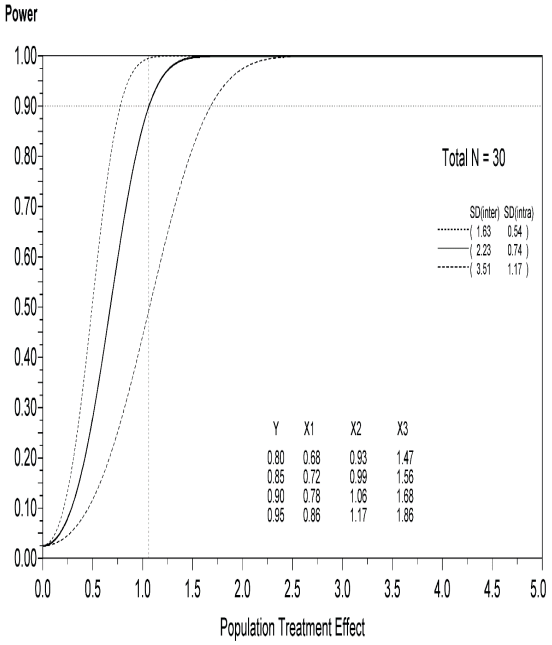


Figure 8 EY_1_2_6789



10.4 RANDOMIZATION AND BLINDING

10.4.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

Participants will be randomized into one of four treatment-sequence groups. The randomization assignment will occur prior to beginning the initial 5 days of stimulation, once the participant has passed the screening sessions. The randomization will be as follows: tACS and tACS, tACS and sham, sham and sham, sham and tACS. This is a double blind study, so neither the participant nor the researcher will know which treatment treatment-sequence group the participant has been assigned to.

A Frohlich Lab member (Angel Huang) will randomize 40 codes which will be used by the study coordinator and research assistants. These codes will be randomized prior to recruitment of any participants. These codes are directly linked to which treatment regimens the participants receive (sham (*S*) or 10Hz tACS (*A*)).

The codes will be randomized using a randomization function available in MATLAB software. A condition will be included so that the same condition will not be assigned to adjacent participants 3 times in a row. The participant randomization will also be stratified on sex, in that separate randomization schedules will be created for each sex. A total of 40 codes will be randomized for each sex because it is possible that there will be, for example, 35 men and only 5 women.

Angel Huang will have no other responsibility in the study other than providing these randomized codes. The master list containing the condition and the codes will be kept solely by Angel Huang.

Angel Huang will provide the study coordinators an Excel document with the blinded randomized codes. This document will remain on the secure lab drive. The study coordinator will enter the participant's study ID next to their randomization code on the first day of stimulation.

(The CONSORT Statement notes that "Allocation concealment is a technique used to prevent selection bias by concealing the allocation sequence from those assigning participants to intervention groups, until the moment of assignment." Randomization without allocation concealment is not reliable randomization.)

10.4.2 EVALUATION OF SUCCESS OF BLINDING

Blinding will be evaluated using the Adverse Events Questionnaire which will be administered after each stimulation session. On day 5 of stimulation and at the final study session, we will also ask the participant whether they believe they have received stimulation.

10.4.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

This is a double blind clinical trial. The participant and researchers will remain blinded to stimulation conditions through the completion of data collection. In the event of an AE/SAE, the PI will be able to determine the stimulation condition of the participant.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Human Research Committee (IRB):

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

Informed Consent:

- Initial consent documented in REDCap via eConsent form.
- Ensure that participant identification is on all pages of the physical copy of the ICF.
- 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 G)* made for any informed consent deviations.
- Ensure a valid (current version date) copy of the consent form was used.

Protocol:

- Confirm that the study staff is conducting the study in compliance with the protocol approved by IRB
- The protocol deviations (exceptions and violations) are documented in the participant chart and reported to IRB as required.

Source Documents:

- Each participant binder will contain a checklist to ensure that each binder has each source document. The checklist will be dated by the researcher for each time an assessment is administered.
- Review participant charts 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 G)* are made for missing or incomplete data and to explain any discrepancies or additional comments.

Electronic Case Report Forms (eCRF)

- Ensure the data reported on the eCRF is consistent with the source documents.
- Discrepancies between the source documents and eCRF are explained in a note to file *(Appendix G)* or captured in a comment in the eCRF.

DNA

- Participant names will not be on any of the samples collected at the initial session. DNA testing is performed within the University of North Carolina at Chapel Hill and the samples are not shared with or processed by any third party outside the university.

The research coordinator, research assistants, and PI will have access to all of the above information. Co-I/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. The key linking dummy identifiers with subject information will be securely destroyed after completion of data acquisition.

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 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).

12.2 INSTITUTIONAL REVIEW BOARD

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

1. The rights and welfare of human participants are paramount in the research process;
2. The highest standards of ethical conduct are employed in all research involving human participants;
3. Research investigators are properly trained in the ethical and regulatory aspects of research with human participants;
4. 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

Research using human participants at UNC-Chapel Hill conforms to all applicable local, state, and federal laws and regulations and the policies of the university.

12.3 INFORMED CONSENT PROCESS

12.3.1 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. eConsent documentation via REDCap is required prior to the administration of any assessments used in this study. A physically signed consent form describing, in detail, the study intervention, device, procedures, and risks will be provided to the participant. Written documentation of informed consent is required prior to the administration of any treatment used in this study. All consent forms will be IRB-approved and updated with any new information as modifications are made throughout the study.

12.3.2 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 complete the eConsent form via REDCap before any verbal assessments take place. Participants must sign the physical informed consent document prior to any additional study 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.

12.3.3 EXCLUSION OF SPECIAL POPULATIONS

Non-English speaking individuals are excluded because the ability to accurately and completely 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 1st day of stimulation in order to determine eligibility for the study.

12.4 PARTICIPANT AND DATA 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.

12.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

12.5 FUTURE USE OF STORED SPECIMENS

No specimen samples will be stored.

12.5 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.

13 DATA HANDLING AND RECORD KEEPING

13.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

The study coordinator and research assistants are responsible for the accuracy, completeness, legibility, and timeliness of the data reported. Any changes made to the data will involve crossing out the original data, documenting the new data with the initials and date of the researcher making the change.

The responsibilities designated to each member of the research team are documented on the Delegation of Authority Log (*Appendix F).* 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. Dr. Fred Jarskog will be the medical monitor for the study.

13.2 DATA CAPTURE METHODS

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.

Data will be collected in the form of MR scan images. Images will be labeled using a unique study identifier and the subject's DOB only. MR images will be stored on a secure PACS server that is only accessible to the employees affiliated with the study. Those people affiliated with the study, will be able to access the MR images off the PACS server. Occasionally, images will be put onto CD or DVD to be passed between research team members. CDsor DVDs will only contain MR images with a DOB and unique study identifier. CDs or DVDs will only be passed between research personnel by hand.

13.3 TYPES OF DATA

Data will be collected to determine eligibility. During the initial session, the SCID, C-SSRS, AHRS, PANSS, CGI-S, SAS and AIMS will be administered. In order to participate in this study, the participant must have a diagnosis of

schizophrenia or schizoaffective disorder, experience medication refractory auditory hallucinations, and are currently not committed in an inpatient hospital and on stable medication.

We will also be collecting data to assess cognitive abilities at the 1st day of stimulation, the 5th day of stimulation and end point (one month follow-up). The BACS will be used to assess cognition in each participant and will be used as a safety monitor and data collection tool to monitor any changes throughout the course of the study.

The stimulation adverse effects questionnaire will be administered after each stimulation in order to monitor any side effects the participant may experience from the stimulation treatment. After the last stimulation and at the one week and one month follow-up, participants will be asked whether they believe their symptoms have improved due to treatment.

The AHRS will be our primary outcome for this study. We will administer this questionnaire at the initial session, on the 1st day of stimulation, the 5th day of stimulation, and the one week and one month follow up. As our primary outcome, the data we collect with the AHRS will be used to evaluate the efficacy of treatment.

The PANSS and the BACS will be used to collect additional data throughout the study. These questionnaires will also be administered on the 1st day of stimulation, the 5th day of stimulation, and at the final session.

An EEG recording will be performed at the 1st day of stimulation, the 5th day of stimulation, and at the 1st, 3rd and final maintenance sessions. The data collected from the EEG recording will enable assessment of neurophysiological changes induced by stimulation.

ECG recordings will be collected at the 1st day of stimulation, the 5th day of stimulation, and at the 1st, 3rd, and final maintenance sessions.

sMRI data will be collected during the week between the 5th day of stimulation and the 1st maintenance session. Eligibility to complete the study will not be determined by sMRI data collection. If the participant is unwilling or unable to complete the MRI scan, they will be allowed to continue participation.

13.4 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 or grant end date, whichever is later.

13.5 PROTOCOL DEVIATIONS

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

13.6 PUBLICATION AND DATA SHARING 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 (NIMH) 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, highly-ranked psychiatry journal.

14 STUDY ADMINISTRATION

14.1 STUDY LEADERSHIP

Principal Investigator: Dr. Flavio Frohlich, PhD

Co-I: Dr. Fred Jarskog, MD

Co-I: Dr. John Gilmore, MD

Study Coordinator: Rachel Force, PhD

15 LITERATURE REFERENCES

Ali, M. M., K. K. Sellers, et al. (2013). "Transcranial alternating current stimulation modulates large-scale cortical network activity by network resonance." The Journal of neuroscience: the official journal of the Society for Neuroscience 33(27): 11262-11275.

Antal, A., Chaieb, L., Moliadze, V., Monte-Silva, K., Poreisz, C., Thirugnanasambandam, N., & Paulus, W. (2010). Brain-derived neurotrophic factor (BDNF) gene polymorphisms shape cortical plasticity in humans. *Brain Stimulation*, *3*(4), 230-237. doi:10.1016/j.brs.2009.12.003

Arns, M., C. K. Conners, et al. (2013). "A decade of EEG Theta/Beta Ratio Research in ADHD: a meta-analysis." J Atten Disord 17(5): 374-383.

Berlim, M.T., Van den Eynde, F., and Daskalakis, Z.J. (2013). Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Journal of psychiatric research 47, 1-7.

Bigdely-Shamlo, N., et al. (2015). "The PREP pipeline: standardized preprocessing for large-scale EEG analysis." Front Neuroinform 9: 16. Delorme A & Makeig S (2004) EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics, Journal of Neuroscience Methods

Brunelin, J., M. Mondino, et al. (2012). "Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia." Am J Psychiatry 169(7): 719-724.

Brunoni, A. R., J. Amadera, et al. (2011). "A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation." The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum 14(8): 1133-1145.

Brunoni, A. R., M. A. Nitsche, et al. (2012). "Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions." Brain stimulation 5(3): 175-195.

Cohen, M. X., N. Axmacher, et al. (2009). "Good vibrations: cross-frequency coupling in the human nucleus accumbens during reward processing." Journal of cognitive neuroscience 21(5): 875-889.

da Silva, T. L. and A. V. Ravindran (2015). "Contribution of sex hormones to gender differences in schizophrenia: A review." Asian J Psychiatr 18: 2-14.

Delorme, A. and S. Makeig (2004). "EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis." Journal of neuroscience methods 134(1): 9-21.

Egan M.F., Kojima M., Callicott J.H., Goldberg T.E., Kolachana B.S., Bertolino A., et al. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell, 112(2), pp. 257–269. doi:10.1016/S0092-8674(03)00035-7

First, M. B., & Gibbon, M. (2004). The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II). In M. J. Hilsenroth, D. L. Segal (Eds.) , Comprehensive handbook of psychological assessment, Vol. 2: Personality assessment (pp. 134-143). Hoboken, NJ, US: John Wiley & Sons Inc.

Fritsch, B., J. Reis, et al. (2010). "Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning." Neuron 66(2): 198-204.

Fröhlich F, McCormick DA.. Endogenous electric fields may guide neocortical network activity. Neuron(2010) 67:129–43.10.1016/j.neuron.2010.06.005

Frohlich, F. and S. L. Schmidt (2013). "Rational design of transcranial current stimulation (TCS) through mechanistic insights into cortical network dynamics." Frontiers in human neuroscience 7: 804.

Green, M. F., R. S. Kern, et al. (2000). "Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"?" Schizophrenia bulletin 26(1): 119-136.

Gonzalez-Rosa, J. J., Soto-Leon, V., Real, P., Carrasco-Lopez, C., Foffani, G., Strange, B. A., & Oliviero, A. (2015). Static Magnetic Field Stimulation over the Visual Cortex Increases Alpha Oscillations and Slows Visual Search in Humans. J Neurosci, 35(24), 9182-9193. doi:10.1523/JNEUROSCI.4232-14.2015

Hariri, A. R., Goldberg, T. E., Mattay, V. S., Kolachana, B. S., Callicott, J. H., Egan, M. F., & Weinberger, D. R. (2003). Brain-Derived Neurotrophic Factor val^{66} met Polymorphism Affects Human Memory-Related Hippocampal Activity and Predicts Memory Performance. The Journal Of Neuroscience, 23(17), 6690-6694.

Jarskog, L. F., R. M. Hamer, et al. (2013). "Metformin for weight loss and metabolic control in overweight outpatients with schizophrenia and schizoaffective disorder." The American journal of psychiatry 170(9): 1032-1040.

Kanai, R., L. Chaieb, et al. (2008). "Frequency-dependent electrical stimulation of the visual cortex." Curr Biol 18(23): 1839-1843.

Kay, S. R., Flszbein, A., & Opfer, L. A. (1987). The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. Schizophrenia Bulletin, 13(2), 261-276.

Keefe, R. S., Goldberg, T. E., Harvey, P. D., Gold, J. M., Poe, M. P., & Coughenour, L. (2004). The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophrenia Research, 68(2-3), 283-297. doi:10.1016/j.schres.2003.09.011

Keefe, R. E., Poe, M., Walker, T. M., & Harvey, P. D. (2006). The Relationship of the Brief Assessment of Cognition in Schizophrenia (BACS) to Functional Capacity and Real-world Functional Outcome. Journal Of Clinical And Experimental Neuropsychology, 28(2), 260-269. doi:10.1080/13803390500360539

Keefe, R. S., C. E. Eesley, et al. (2005). "Defining a cognitive function decrement in schizophrenia." Biological psychiatry 57(6): 688-691

Keefe, R. S., R. W. Buchanan, et al. (2013). "Clinical trials of potential cognitive-enhancing drugs in schizophrenia: what have we learned so far?" Schizophrenia bulletin 39(2): 417-435.

Kirkpatrick, B., W. S. Fenton, et al. (2006). "The NIMH-MATRICS consensus statement on negative symptoms." Schizophrenia bulletin 32(2): 214-219.

Kleim, J. A., Chan, S., Pringle, E., Schallert, K., Procaccio, V., Jimenez, R., & Cramer, S. C. (2006). BDNF val66met polymorphism is associated with modified experience-dependent plasticity in human motor cortex. Nature Neuroscience, 9(6), 735-737. doi:10.1038/nn1699

Kutchko, K. M. and F. Frohlich (2013). "Emergence of metastable state dynamics in interconnected cortical networks with propagation delays." PLoS computational biology 9(10): e1003304.

Lawrie, S. M., C. Buechel, et al. (2002). "Reduced frontotemporal functional connectivity in schizophrenia associated with auditory hallucinations." Biol Psychiatry 51(12): 1008-1011.

Miniussi, C., D. Brignani, et al. (2012). "Combining transcranial electrical stimulation with electroencephalography: a multimodal approach." Clin EEG Neurosci 43(3): 184-191.

Neuling, T., S. Rach, et al. (2013). "Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states." Frontiers in human neuroscience 7: 161.

Nitsche, M. A., W. Jaussi, et al. (2004). "Consolidation of human motor cortical neuroplasticity by D-cycloserine." Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 29(8): 1573-1578.

Nitsche, M. A. and W. Paulus (2000). "Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation." The Journal of physiology 527 Pt 3: 633-639.

Pezawas L.,Verchinski B.A., Mattay V.S., Callicott J.H., Kolachana B.S., Straub R.E., Egan M.F., Meyer-Lindenberg A, Weinberger D.R. (2004). “The Brain-Derived Neurotrophic Factor val66met Polymorphism and Variation in Human Cortical Morphology.” The Journal of Neuroscience 24 (45): 10099–102. doi:10.1523/JNEUROSCI.2680-04.2004.

Polania, R., M. A. Nitsche, et al. (2012). "The importance of timing in segregated theta phase-coupling for cognitive performance." Curr Biol 22(14): 1314-1318.

Scherk M (1990), "Fundamentals of dipole source potential analysis". In: "Auditory evoked magnetic fields and electric potentials" (eds. F. Grandori, M. Hoke and G.L. Romani). Advances in Audiology, Vol. 6.

Seth, A. K. (2010). "A MATLAB toolbox for Granger causal connectivity analysis." Journal of neuroscience methods 186(2): 262-273.

Shergill, S. S., R. M. Murray, et al. (1998). "Auditory hallucinations: a review of psychological treatments." Schizophrenia research 32(3): 137-150.

Silbersweig, D. A., E. Stern, et al. (1995). "A functional neuroanatomy of hallucinations in schizophrenia." Nature 378(6553): 176-179.

Stagg, C. J. and M. A. Nitsche (2011). "Physiological basis of transcranial direct current stimulation." Neuroscientist 17(1): 37-53.

Uhlhaas, P. J. and W. Singer (2012). "Neuronal dynamics and neuropsychiatric disorders: toward a translational paradigm for dysfunctional large-scale networks." Neuron 75(6): 963-980.

van der Leeuw, C., Habets, P., Gronenschild, E., Domen, P., Michielse, S., van Kroonenburgh, M., van Os, J., Marcelis, M., and for, G.R.O.U.P. (2013). Testing the estrogen hypothesis of schizophrenia: associations between cumulative estrogen exposure and cerebral structural measures. Schizophr Res *150*, 114-120

van Rooijen, R., Ploeger, A., & Kret, M. E. (2017). The dot-probe task to measure emotional attention: A suitable measure in comparative studies? Psychon Bull Rev. doi:10.3758/s13423-016-1224-1

Vicente, R., M. Wibral, et al. (2011). "Transfer entropy--a model-free measure of effective connectivity for the neurosciences." Journal of computational neuroscience 30(1): 45-67.

Winterer, G., R. Coppola, et al. (2003). "Functional and effective frontotemporal connectivity and genetic risk for schizophrenia." Biological psychiatry 54(11): 1181-1192.

Zaehle, T., S. Rach, et al. (2010). "Transcranial alternating current stimulation enhances individual alpha activity in human EEG." PloS one 5(11): e13766.

Zaghi, S., M. Acar, et al. (2010). "Noninvasive brain stimulation with low-intensity electrical currents: putative mechanisms of action for direct and alternating current stimulation." The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry 16(3): 285-307.

APPENDIX A: 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)

_____
_____
_____
_____

CI signature _____Date_____

PI Comments:

_____
_____
_____
_____
_____

Steps to be taken (if applicable)

_____
_____
_____
_____

PI signature _____Date_____

APPENDIX B: AE LOG

Participant ID	**√ if AE meets definition of serious***	**Grade and 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			

APPENDIX C: SAE REPORT FORM

Participant ID: _____

1. Location of SAE (e.g., clinic, home): _____

2. Age: _____

3. Gender: Male Female

4. SAE term (provide diagnosis): _____

4a. If diagnosis is not known, symptoms: _____

5. Date of onset: _____ (dd/mm/yyyy)

6. What is the severity grade of the serious adverse event?

☐ Grade: 1: Mild

☐ Grade 2: Moderate

☐ Grade 3: Severe

☐ Grade 4: Life-threatening

☐ Grade 5: Death

7. Did the participant receive the investigational product or study intervention prior to this SAE?

☐ Yes ☐ No ☐ N/A

7a. If yes, identify the investigational product or study intervention received prior to the SAE:

Investigational Product/Study Intervention

Dose_____

Units_____

Frequency_____

Start Date _____/_____/_____(dd/mm/yyyy)

Stop Date _____/_____/_____((dd/mm/yyyy)

Check if Ongoing ☐

8. Action taken with investigational product/study intervention:

☐ Continued

☐ Lowered

☐ Interrupted

☐ Discontinued

☐ Increased

N/A

9. Outcome of SAE:

☐ Ongoing at this time

☐ Resolved without sequelae

Resolved with sequelae

☐ Death

☐ Present at death, not contributing to death

10. Date of resolution: _____ (dd/mm/yyyy) or

☐ Ongoing at end of study

11. Seriousness criteria? (Check all that apply)

☐ Life-threatening

☐ Required hospitalization or

☐ Prolongation of existing hospitalization

Congenital anomaly

☐ Disabling/incapacitating

☐ Important medical event

Fatal

If fatal: 11a. Date of death: _____ (dd/mm/yyyy)

11b. Primary cause of death: _____

11c. Was an autopsy performed?

☐ Yes

No

12. Relationship to investigational product/study intervention:

☐ Related (Associated with the use of the study intervention. There is a reasonable possibility that the experience may have been caused by the study intervention.)

☐ Unrelated

13. If SAE is unrelated to investigational product/safety intervention, select all possible etiologies:

Concurrent illness, disease, or other external factors, specify:

_____

Concurrent medication, specify:

_____

Secondary study procedure, specify:

_____

Accident, trauma, or other external factors, specify:

_____

Other, specify:

_____

14. Did the participant receive any relevant concomitant medications in response to the SAE?

☐ Yes
☐ No

14a. If yes, please specify: Name, Start and Stop date or On going

_____

15. Did the participant receive any treatments/procedures in response to the SAE?

☐ Yes
☐ No

15a. If yes, please specify

_____

_____

16. Did the participant receive relevant laboratory or diagnostic tests in response to the SAE?

Yes

No

16a. If yes, provide the name of the test and results with normal ranges and/or supplemental exams below:

_____

_____

17. Narrative/Comments (provide a description of the serious adverse event including chronological clinical presentation and evolution of the serious adverse event and associated signs/symptoms):

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

18. Completion of form: printed names, signatures and date of signature

Person Completing Form (print name) *Person Completing Form (signature)* *Date*

_____

Investigator (print name) *Investigator (signature)* *Date*

_____

APPENDIX D: UE/SAE LOG

Participant ID	Date Event Occurred	Date Study Team Notified of Event	Event	Date Reported to IRB	Study SAE Form Completed
					☐Yes ☐No ☐N/A
					☐Yes ☐No ☐N/A
					☐Yes ☐No ☐N/A
					☐Yes ☐No ☐N/A
					☐Yes ☐No ☐N/A

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 in 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 F: DELEGATION OF AUTHORITY

Designee (full name)					
Title & Position					
Delegated Activity (see codes)					
Designee Signature & Dates					
Designee Initials (signed)					
	Activity Codes: 1: Informed consent process 5: Creation of randomization codes 9: Stimulation waveform verification 13: Clinical responsibility 2: Eligibility verification 6: tACS Administration 10: Safety monitoring 3: Questionnaire administration 7: EEG Administration 11: AE/UE assessment 4: Training of study procedures 8: Data Entry 12: AE/UE Documentation/Reporting				
	Investigator's Authorization: I hereby delegate the above significant research-related duties to the following persons and understand that the overall responsibility for conduct of the research remains with me. [1]Investigator's Signature: Date:				

APPENDIX G: NOTE TO FILE

IRB#: 17-1364 PI: Flavio Frohlich

Study Title: _____

Date of Occurrence: _____

Research Name: _____

Participant ID: _____

Reason for Note: _____
_____

Note:
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Corrective action (if applicable);_____
_____
_____
_____

Signature: _____ Date: _____

APPENDIX H: PROTOCOL DEVIATION LOG

Participant ID	Date Occurred	Description	CAPA*	Date PI Notified	Date IRB Notified	PI Initial/Date

APPENDIX I: TRAINING LOG

IRB Number: 17-1364 **PI: Flavio Frohlich, Phd**

1	Protocol	3	EEG application	5	Data Entry
2	Questionnaire Administration	4	Stimulation	6	Other (Specify)

By signing, each staff member verifies he/she has been trained on the information and understand the obligations/responsibilities associated with this training.

Training Date	Trainee Name (please print)	Trainee Signature	Training Format (e.g., Presentation, Self-Study)	Trainer Initials

APPENDIX J: TELEPHONE RECRUITMENT SCRIPT

Hello, my name is _____ and I am contacting you because you were seen by UNC Health Care or one of our affiliate hospitals or clinics in the past year. I am a study coordinator from the University of North Carolina at Chapel Hill conducting a research study regarding brain activity in schizophrenia. Your records in the UNC Health Care System indicate you may be eligible to participate in our research study OR 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 participate 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)

First, I need to ask for your verbal consent to conduct the screening interview. I will ask questions about your age, medication use, psychiatric diagnosis, and personal health history. You may decline to answer any questions, but please keep in mind that this may affect our ability to determine if you qualify for the initial session of the study. Of course, the information you provide is strictly confidential, and will not be used for any purpose other than eligibility. Do you consent to participate in the screening interview?

(If 'No', thank them for their time and hang up.)
(If 'Yes', proceed.)

Great! This study is looking at how abnormal rhythms of brain activity in schizophrenia respond to very weak applied currents. Findings from this study will help the development of treatments for the symptoms of schizophrenia, like auditory hallucinations. In the study, a very weak 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 1 to 18 sessions, with one session being an initial screening session, three possible follow-up screening sessions, then five, twice daily stimulation sessions, followed by a session for an MRI scan and 8 weeks of once weekly stimulation sessions. The five days of stimulation sessions need to be on consecutive days preferably Monday through Friday, with the second session occurring 3 hours after the completion of the first session. The maximum compensation for this study is $760 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 (i.e. epilepsy)? (No)
- Are you currently taking any benzodiazepines? (No)
    - What medications are you currently prescribed?

- Do you use any drugs or medications not prescribed, including marijuana, cocaine, etc.? (No)
    - Please note that we will conduct a urine drug test at the initial screening session.
- 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? (No)
- (For females only), Is there a chance you may be pregnant? (No)
- Have you ever been diagnosed with a mental or psychiatric illness by a professional (i.e. a psychiatrist or other licensed clinician)? (Yes)
    - If yes: What were you diagnosed with?
- Do you ever experience auditory hallucinations (i.e. hearing voices or noises no one else can hear)? (Yes)
    - If yes: On average how often does this happen per week?

Follow-up questions:

- Do you wear glasses/contact lenses?
    - Could you bring your contact lenses for the study visits instead of wearing your glasses?

(If answered according to all indicated responses, continue)

Excellent! Due to the study schedule, some sessions will be longer than others. Is it possible for you to be available from 8 – 5 on weekdays to be at the UNC Hospital in order to participate in this study? If not, can you specify the days/times that do not work for you?

Would you be willing to participate in a 7 hour session for this study? (This includes a 3 hour break).

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. I'd like to schedule your first session now. It will last approximately 3 hours. All testing will be conducted at either UNC Hospital or the NCPRC in Raleigh. (specific location).

(Schedule a time for first session)

I will give you a call to confirm your appointment 24 hours beforehand. If you have any questions before then, please don't hesitate to contact us at this phone number.

Thank you for your time.