TARGETING AUDITORY HALLUCINATIONS WITH ALTERNATING CURRENT STIMULATION

IRB # 14-3285

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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.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Signed: _____ Date: _____

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LIST OF ABBREVIATIONS

ACT	Assertive Community Treatment
AE	Adverse Event
AHRS	Auditory Hallucination Rating Scale
AIMS	Abnormal Involuntary Movement 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
CGI-S	Clinical Global Impression Severity Scale
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
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
Hz	Hertz
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
NCPRC	North Carolina Psychiatric Research Center
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
SAS	Simpson Angus Scale

SCID	Structured Clinical Interview for DSM-IV Axis I Disorders
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

PROTOCOL SUMMARY

Title:	Targeting Auditory Hallucinations with Alternating Current Stimulation
Précis:	The purpose to determine the efficacy of transcranial alternating current stimulation, tACS, versus sham stimulation (with tDCS versus sham as a positive control for assay sensitivity) for the treatment of medication-refractory auditory hallucinations in patients with schizophrenia. We will recruit 48 males and females diagnosed with schizophrenia or schizo-affective disorder. Eligible participants will have 5, twice-daily (one week Monday through Friday), 20 minute stimulation sessions. Stimulations will be at least 3 hours apart. Participants will be randomly assigned to one of three groups; sham stimulation, 10 Hz (alpha) tACS or 2 mA tDCS. Participation will involve 1 to 8 visits. At the initial session, informed consent will be obtained and subjects will be screened for eligibility. Eligible participants will then be scheduled for their, twice-daily stimulation sessions which will include daily assessment of stimulation side-effects. Clinical assessments will be performed at baseline, 1, 2 and 4 weeks using the Auditory Hallucinations Rating Scale *(Attachment 3)*. Neurophysiological (EEG) and cognitive assays will be performed before and after stimulation. *Please see Appendix A for a detailed schematic describing all visits and assessments.*
Objectives:	Our primary objective is to demonstrate the value of synchronization and information flow 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 synchronization and information flow predicts treatment success and (2) changes in these markers correlate with improvement of clinical symptom presentation as determined by the AHRS, PANSS, and BACS *(Attachment 12)*. We will test our working hypothesis by measuring whole-head EEG data from all patients in our feasibility study (48 patients from Aim 1) before and

	immediately after the five day course of stimulation and at both follow-up visits.
Population:	We will recruit 48 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 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:	Pilot Study
Number of Sites:	This is a single site study performed at University of North Carolina- Chapel Hill.
Study Duration:	This study will take 2 years to complete
Participant Participation Duration:	Eligible participants who complete this clinical trial will have a total of 8 visits; an initial session, 5 days of twice-daily stimulation, a one week and a one month follow up visit (Follow up sessions are measured from last day of stimulation). The initial screening session will take approximately 3 hours, each follow up screening session will last approximately 2 hours, the first day of stimulation will take approximately 6 hours. Days 2 through 4 of stimulation will take 4.5 hours each day. Day 5 of stimulation will last about 9 hours. The one week follow up will take approximately 2.5 hours and the one month follow up will take approximately 5 hours. We estimate that total participation to be approximately 40 hours.
Description of Agent or Intervention:	We will be using an active sham, 10 Hz tACS and 2mA tDCS. Active sham treatment will include 10 seconds of ramp in to 1 minute of 10 Hz tACS with a ramp out of 10 seconds for a total of 80 seconds of stimulation. The choice of an active sham is motivated to enhance success of patient blinding by mimicking skin sensations associated with tACS. Both 10 Hz tACS and tDCS will also have a 10 second ramp in and ramp out with 20 minutes of stimulation for a total of 1180 seconds. Stimulation waveforms are sine-waves with a peak-to-peak amplitude of 2 mA.
Estimated Time to Complete Enrollment:	We estimate that it will take 2 years to complete enrollment of participants.

***Schematic of Study Design:**

Table 1. The 48 participants will be randomized into one of three of the following arms

ARM 1	16 participants	Sham
ARM 2	16 participants	10 Hz tACS
ARM 3	16 participants	tDCS

* Weeks are based on time from last stimulation session

Initial Screening Session	2nd Screening Session	3rd Screening Session	4th Screening Session	Day 1 of stimulation	Days 2-4 of Stimulation	Day 5 of Stimulation	One Week Follow Up	One Month Follow Up
•Administer SCID to confirm eligibility - 45 mins •Demographics and Medications are recorded - 5 mins •Vital Signs are taken - 5 mins •Participants asked to complete Urine Drug Screen - 5 min •beta-HCG[a]- 5 mins •AHRS is administered- 10 mins •Schedule 2nd Screening Session **•2 hours**	•Vital signs taken - 5 mins •EEG - 100 mins •AHRS administered - 10 mins •(if AHRS score stable) SAS administered - 10 mins •(if AHRS score stable) AIMS administered - 10 mins •(if AHRS score stable) BDNF saliva sample collected - 1 min •(if AHRS score stable) schedule week of stimulation •(if AHRS score not stable) Schedule 3rd screening session **•3 hours**	•Vital signs taken - 5 mins •EEG - 100 mins •AHRS administered - 10 mins •(if AHRS score stable) SAS administered - 10 mins •(if AHRS score stable) AIMS administered - 10 mins •(if AHRS score stable) BDNF saliva sample collected - 1 min •(if AHRS score stable) schedule week of stimulation •(if AHRS score not stable) Schedule 4th screening session **•3 hours**	•Vital signs taken - 5 mins •EEG - 100 mins •AHRS administered - 10 mins •(if AHRS score stable) SAS administered - 10 mins •(if AHRS score stable) AIMS administered - 10 mins •(if AHRS score stable) BDNF saliva sample collected - 1 min •(if AHRS score stable) schedule week of stimulation •(if AHRS score not stable) Participant is not eligible to participate **•3 hours**	•Vital signs taken - 5 mins •AHRS is administered - 10 mins •PANSS is administered - 60 mins •BACS is administered - 30 mins •CGI-S is administered - 5 min •20 minute stimulation (active or sham) - 40 mins •Adverse Events Questionnaire - 1 min •------3 hours Break--------- •20 minute stimulation 3 hours after first stimulation (active or sham)- 40 mins •Adverse Events questionnaire- 1 min **•6 hours**	•Vital signs taken - 5 mins •20 minute stimulation (active or sham stimulation) - 40 mins •Adverse Events Questionnaire- 1 min •--------3 hour Break--------- •20 minute stimulation 3 hours after first stimulation (active or sham)- 40 mins •Adverse Events Questionnaire- 1 min **•4.5 hours**	•Vital signs taken- 5 mins •EEG- 100 mins •20 minutes of stimulation (active or sham)- 40 mins •Adverse Events Questionnaire- 1 min •--------3 hour Break--------- •20 minutes of stimulation 3 hours after first stimulation (active or sham)- 40 mins •Adverse Events Questionnaire - 1 min •AHRS administered- 10 mins •PANSS administered- 60 mins •BACS is administered- 30 mins •CGI-S is administered- 5 min •SAS is administered- 10 mins •AIMS is administered- 10 mins **•9 hours**	•Vital signs taken-5 mins •EEG-100 mins •AHRS is administered - 10 mins •Symptom Improvement Quesionnaire- 1 min **•2.5 hours**	•Vital signs taken-5 mins •EEG-100 mins •AHRS is administered - 10 mins •Symptom Improvement Quesionnaire- 1 min •Medications are recorded- 5 mins •PANSS administered- 60 mins •BACS is administered - 30 mins •CGI-S is administered - 5 min •SAS is administered - 10 mins •AIMS is administered- 10 mins **•5 hours**

1 KEY ROLES

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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 coherence) 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 coherence and information flow between key brain regions. 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.

2.3 Potential Risks and Benefits

2.3.1 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 locked rooms, separate from any source documents containing participant dummy identifiers. All data is stored in locked cabinets inside locked offices; electronic data will be stored only on password-protected computers, and data encryption methods will be used during communication between investigators. Only study personnel will have access to these data. All study staff participate in annual human participant training that includes education about responsibilities to the minimize risk of confidentiality breach.

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 determine whether these effects were experienced. Research personnel present during these sessions will also check in with the participant periodically during the stimulation to see whether they are comfortable. If any side-effect occurs (rated by the participant as stronger than "moderate") or the participant is experiencing severe discomfort, the stimulation will be immediately stopped.

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.

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

3.1 Study Objectives

Our primary objective is to develop an effective non-invasive brain stimulation paradigm that will treat medication refractory auditory hallucinations in patients with schizophrenia.

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

The Auditory Hallucination Rating Scale *(Attachment 3)* will be the primary outcome measure for this study. This rating will be administered at baseline, two weeks later at the screening visit, the first day of stimulation, last day of stimulation, at the one week and the one month follow up visits. We will compare the AHRS scores immediately before the first stimulation session and immediately after the last stimulation session as our primary outcome measure.

3.2.2 Secondary Outcome Measures

We will compare alpha oscillation power from resting state EEG recordings from the screening visit and last day of stimulation. We will also collect EEG data at the one week and one month follow up visits. We will use these data to analyze alpha frequency activity as a pilot study for derivation of EEG biomarkers.

The Positive and Negative Syndrome Scale (PANSS) *(Attachment 5)* and Brief Assessment of Cognition in Schizophrenia (BACS) *(Attachment 12)* will also be secondary outcome measures for this study. These measurements will be taken at baseline, first day of stimulation, and last day of stimulation and at the one month follow up visit. We will compare the PANSS and BACS scores immediately before first stimulation session and immediately after last stimulation session as secondary outcome measures.

4 STUDY DESIGN

The design for this pilot study is a randomized, double blind, sham-controlled, clinical trial which will be used to demonstrate feasibility and collect preliminary efficacy data for further refinement of a tACS approach. We are recruiting from a clinical population. For this clinical trial we are seeking 48 males and non-pregnant females ages 18-70 with 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 and have been clinically stable for at least 12 weeks, meaning no change in their level of care. All women of child-bearing potential will have a pregnancy test during the initial session in order to determine eligibility for the study. These individuals 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.

This is a single site, clinical trial with 3 arms. We estimate 2 years to complete study enrollment.

Participants will be randomly assigned to one of three arms; active sham stimulation, 10 Hz (alpha) tACS or 2 mA tDCS. Active sham treatment will include 10 seconds of ramp in to 1 minute of 10 Hz tACS with a ramp out of 10 seconds for a total of 80 seconds of total stimulation. The choice of an active sham is motivated to enhance success of patient blinding by mimicking skin sensations associated with tACS. 10 Hz and 2 mA tDCS will have a 10 second ramp in and ramp out with 20 minutes of stimulation for a total of 1180 seconds twice daily for one week. Stimulation waveform is a sine-wave with a peak-to-peak amplitude of 2 mA. In each arm, participants will stay in a relaxed and yet controlled state by watching a nature movie such as “Reefscape” during stimulation.

Eligible participants who complete this clinical trial will have a total of 9 to 11 visits; an initial screening session, a 2nd screening session, (if needed) 2 more follow up screening sessions, 5 days of twice daily stimulation sessions, a one week and a one month follow up visit. The initial screening session will take approximately 2 hours, and each follow up screening session will take approximately 3 hours each. The first day of stimulation will take approximately 6 hours and days 2 through 4 of stimulation will take 4.5 hours each. The last day of stimulation will take about 9 hours. The one week follow up will take approximately 2.5 hours and the one month follow up will take approximately 5 hours. We estimate that total participant participation duration will be approximately 41 to 47 hours.

The primary objective is to conduct a pilot clinical trial to establish the feasibility of recruitment and implementation of the methodology and to collect preliminary efficacy data for the use of tACS by comparing AHRS scores immediately before the first stimulation session and

immediately after the last stimulation session in patients with schizophrenia of schizoaffective disorder. As a secondary objective we will assess the differential clinical effects of sham, 10 Hz and 2 mA tDCS on EEG measures of alpha oscillations.

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 least 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 of substance abuse (other than nicotine) within the last month or a DSM-IV diagnosis of alcohol or substance dependence (other than nicotine) within the last 6 months
- 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 caused cognitive sequelae
- A difference of greater than 20% in AHRS scores between Consent Visit and Screening Visit.
- 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 childbearing 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 48 patients with schizophrenia and persistent auditory hallucinations, despite optimized antipsychotic medication treatment for at least 3 months. 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 10 subjects will be enrolled at the UNC-CH location, approximately 24 subjects will be enrolled at the Raleigh site, and approximately 14 subjects will be enrolled through ACT teams, for a total of 48 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 as well as the team that goes to see patients in the community through the ACT program. 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 1 month 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 follow up session. Each research staff member will be easily available for the participants to contact via email or phone. The inclusion criteria state that each participant must be able to understand all risks and benefits associated with this study. We will be asking each participant to answer questions about the consent form to determine that the study process and the duration of participation are completely understood by all participants. We will aim to have a specific research team member assigned to complete all sessions with the same participant. However we will not require the same researcher to be present during stimulation sessions 2 through 4. The study team will work hard at forming 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 more than two non-consecutive sessions. Participants who miss two consecutive sessions will not be eligible to continue their participation.

5.4 Treatment Assignment Procedures

Participants will be randomized into one of three arms. This is a double blind study, so neither the participant nor the researcher will know which treatment arm the participant has been assigned to.

5.4.1 Randomization Procedures

A Frohlich Lab member will randomize 48 codes which will be used by the study coordinator and research assistants. These codes are directly linked to which treatment participants receive (sham, 10Hz tACS or 2 mA tDCS). This lab member will have no other responsibility in the study other than providing these randomized codes.

5.4.2 Reasons for Withdrawal

A study participant will be discontinued from further participation if:

- The participant has missed more than 2 stimulation 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.

5.4.3 Handling of Withdrawals

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. In the case of an early withdrawal, the

researcher will complete a Participant Off Study form to document the withdrawal reason (*Appendix Q).*

5.4.4 Termination 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:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient adherence to protocol requirements.
- Data those 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

We will be using a transcranial current stimulator designed in the Frohlich Lab for investigational research purposes. The device is not implanted and has not been designed for or being used to support or sustain human life. This device does not have a potential for serious risk to the health, safety, or welfare of the participant. There has never been an instance of serious side-effect reported due to use of transcranial brain stimulation. Previous studies in the Frohlich Lab that used comparable devices have always been classified as "non-significant risk" by the UNC IRB.

In addition, some participants will be stimulated with the commercial, CE-certified Neuroconn Plus stimulator (for purely logistic reasons of device availability). The use of this device in this study has previously received a NSR designation on initial review by the full UNC IRB. Both devices are electrically equivalent and provide the same stimulation. 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, maximising 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)

6.1.1 Device Description

The device consists of the following main components/subsystems:

1. Tablet with user interface application (App)
2. Microprocessor
3. Function generator chip
4. Voltage controlled current source
5. Safety circuitry

First, the stimulation parameters are specified by the user through the app. The parameters are:

1. tDCS/tACS
2. Number of channels
3. Amplitude
4. Test duration
5. Frequency (for tACS)
6. Password.

Next, the parameters are sent via Bluetooth to the microprocessor. The microprocessor interprets these parameters, and programs the function generator chip accordingly. The function generator then creates the programmed waveform, which is ultimately a voltage signal. The voltage signal is applied to a voltage controlled current source, which generates the specified amount of current through an arbitrary load resistance.

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

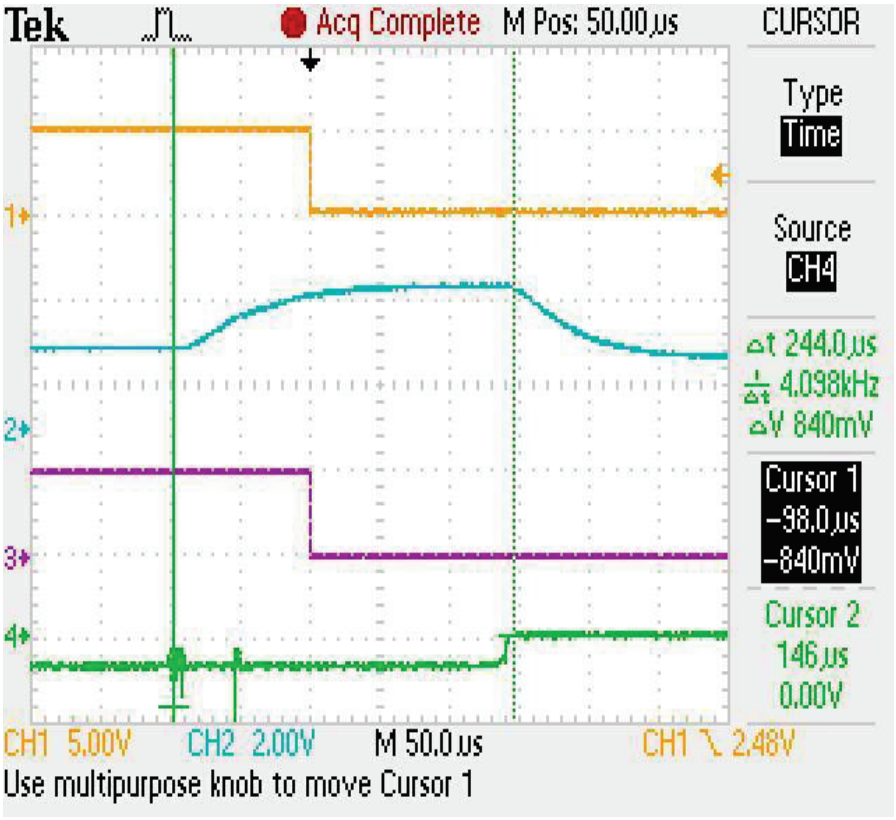
The device is equipped with 4 different stages of safety protection, all of which protect the stimulant from high currents. The stages are as follows:

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.

6.2 Preparation and Administration of Study Investigational Product

After participants have completed the daily questionnaires, they will be comfortably seated. The research team will first measure their heads electrode placement using the 10-20 system. Participants will then be fitted with the 3 electrodes for stimulation. The participant will be in the

relaxed yet, experimentally controlled state by watching a nature movie. One session of stimulation will be performed twice daily, for 20 minutes. In the 10 Hz tACS and 2mA tDCS groups stimulation will have a 10 second ramp in and ramp out with 20 minutes of stimulation for a total of 1220 seconds. Stimulation waveforms are sine-waves with a peak-to-peak amplitude of 2 mA. The sham stimulation will include 10 seconds of ramp in to 1 minute of 10 Hz tACS with a ramp out of 10 seconds for a total of 100 seconds of stimulation. We will be using 5x5cm electrodes covered in 10/20 conductive paste and placed between Fp1 and F3 and between T3 and P3 with a 5x7cm electrode placed over CZ as a return electrode.

Stimulation devices will be preprogrammed and codes will be randomized to one of the three experimental arms. Researchers will enter the participant-specific code into the App that controls the stimulation and monitor participants during the 20 minutes of the stimulation.

The study coordinator and/or the research assistant will be thoroughly trained and have trainings documented on the transcranial stimulation device and will be present during all stimulation sessions. *Please see Appendix S for an example of the training documentation log.* To monitor side effects of stimulation a daily questionnaire will be administered after each stimulation session. *Please see Attachment 1 for an example of the daily stimulation questionnaire, and Attachment 2 for an example of the endpoint stimulation questionnaire.*

6.3 Assessment of Participant Compliance with Study Investigational Product

Compliance for this study includes making all 10 stimulation sessions allowing 2 non-consecutive miss which will be made up the following Saturday. Follow up periods will be able to take place ±3 days of scheduled visits.

7 STUDY SCHEDULE

Drs. Gilmore, Jarskog, Cordle or other approved clinician will be present during the initial session, the 1st day of stimulation, the 5th day of stimulation, and the one month follow up for the first 5 participants, after which the approved clinicians will be present for only the initial session, the 5th day of stimulation and the one month follow up. The approved clinician will be present to administer the SAS *(Attachment 9)*, the AIMS *(Attachment 7)* for each participant and the CGI-S *(Attachment 8)* for the first 5 participants until research personnel are comfortable and certified to do so (will be determined by accompanying clinician). In order to increase data quality, the assessments for an individual participant at the initial session, the 1st day of stimulation, the 5th day of stimulation, the one week one month follow ups will be administered by the same researcher. Protocol for this study will not require the same researcher to be present during days 2 through 4 of stimulation although the team will strive to schedule the same researcher for every session.

7.1 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 and will be filed in the participant binder (*Appendix R*).

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 8 sessions, with 1 initial session, 5 consecutive week days of twice daily stimulation, with follow ups one week after the last stimulation and one month after last 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 telephone script provided in *Appendix T* for all telephone screenings.

- Are you 18 years or older? (Yes)
- Have you ever, or are you currently being treated for a neurological condition (i.e. epilepsy)? (No)

- 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)

7.2 Enrollment/Baseline

Initial Screening Visit (Visit 1, Day 0)
At the consent visit, participants will sign both a HIPAA authorization form and the consent 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. The researcher will verify that the participant meets inclusion criteria. If the participant is female, she will be asked to provide urine for a pregnancy test. All participants (male and female) will be asked to complete a urine drug screening to determine eligibility for the study. Next, the SCID (*Attachment 6*) 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. Once the diagnosis has been confirmed, demographic information will be collected, which will include a history of medication, alcohol, and drug use and information about symptom onset and baseline vitals will be taken. A short handedness questionnaire and a Belief about Treatments questionnaire will also be administered. Each participant will be asked a series of questions (*Appendix H*) to ensure that the consent form is fully understood. After consent has been obtained, a baseline Auditory Hallucinations Rating Scale (AHRS) will be administered to document hallucinatory severity and frequency. The 2nd screening visit will be scheduled for approximately 2 weeks later, and the participant will be paid.

2nd Screening Visit (Visit 2)
At the beginning of the 2nd screening visit, vitals will be taken and an EEG will then be administered. The EEG recording will include resting state data along with two auditory tasks. After each EEG, an EEG questionnaire (*Appendix U)* will be administered to document the participant's auditory experiences during the EEG tasks. 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% then the Simpson Angus Scale (SAS) (*Attachment 9*) and the Abnormal Involuntary Movement Scale (AIMS) (*Attachment 7*) will be administered as a baseline assessment of extrapyramidal syndromes or tardive dyskinesia due to antipsychotic medication use. In order to ensure proper assessment,

each AIMS administration will initially be recorded to be reviewed and scored by Dr. Jarskog until the researcher is deemed to have sufficient experience. At the end of the initial session, and once eligibility has been confirmed, a saliva sample will be collected (for testing of BDNF allele), the week of stimulation will be scheduled, and the participant will be paid.

3rd Screening Visit (Possible Visit 3)

At the beginning of the 3rd screening visit, vitals will be taken and an EEG will then be administered. The EEG recording will include resting state data along with two auditory tasks. After each EEG, an EEG questionnaire (*Appendix U)* will be administered to document the participant's auditory experiences during the EEG tasks. 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% then the Simpson Angus Scale (SAS) (*Attachment 9*) and the Abnormal Involuntary Movement Scale (AIMS) (*Attachment 7*) will be administered as a baseline assessment of extrapyramidal syndromes or tardive dyskinesia due to antipsychotic medication use. In order to ensure proper assessment, each AIMS administration will initially be recorded to be reviewed and scored by Dr. Jarskog until the researcher is deemed to have sufficient experience. At the end of the initial session, and once eligibility has been confirmed, a saliva sample will be collected (for testing of BDNF allele), the week of stimulation will be scheduled, and the participant will be paid.

4th Screening Visit (Possible Visit 4)

At the beginning of the 4th screening visit, vitals will be taken and an EEG will then be administered. The EEG recording will include resting state data along with two auditory tasks. After each EEG, an EEG questionnaire (*Appendix U)* will be administered to document the participant's auditory experiences during the EEG tasks. 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% then the Simpson Angus Scale (SAS) (*Attachment 9*) and the Abnormal Involuntary Movement Scale (AIMS) (*Attachment 7*) will be administered as a baseline assessment of extrapyramidal syndromes or tardive dyskinesia due to antipsychotic medication use. In order to ensure proper assessment, each AIMS administration will initially be recorded to be reviewed and scored by Dr. Jarskog until the researcher is deemed to have sufficient experience. At the end of the initial

session, and once eligibility has been confirmed, a saliva sample will be collected (for testing of BDNF allele), the week of stimulation will be scheduled, and the participant will be paid.

7.3 Stimulation Sessions

Day 1 of Stimulation (Visit 5)
At the first day of stimulation, vitals will be recorded and several questionnaires will be administered. First, the AHRS (*Attachment 3*) will be administered followed by the PANSS (*Attachment 5*) and the Brief Assessment of Cognition in Schizophrenia (BACS) *(Attachment 12)*. 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. After this, the CGI-S (*Attachment 8*) will be administered in order to document any difference in auditory hallucination or symptom severity from the screening visit.

Once the questionnaires are complete, the participant will be administered either sham, 10 Hz tACS or 2 mA tDCS treatment for 20 minutes. Participants will be asked to sit still and not talk during these 20 minutes, and will be asked to keep their eyes open and facing straight ahead. After the 20 minutes of treatment, the participant will be asked to return 3 hours later on the same day for another 20 minutes of either sham, 10 Hz tACS or 2 mA tDCS treatment, where the participant will again be asked to sit still, not talk, and with their eyes open.

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 at the conclusion of this session.

Days 2 – 4 of Stimulation (Visit 6 – 8)
Upon participant arrival, vital signs will be taken and documented at the beginning of the first stimulation session of each day. The participant will then receive 20 minutes of sham, 10 Hz tACS or 2mA tDCS (as per the initial randomization) while sitting quietly with their eyes open. After 3 hours, the participant will return for another 20 minutes of sham, 10 Hz tACS or 2mA tDCS. 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)
Upon participant arrival, vital signs will be taken and documented at the beginning of the first stimulation session of the day. An EEG will then be administered. The EEG recording will include resting state data along with two auditory tasks, and the EEG Questionnaire will be

administered. The participant will receive 20 minutes of sham, 10 Hz tACS or 2mA tDCS (as per the initial randomization) while sitting quietly with their eyes open. After 3 hours, the participant will return for another 20 minutes of sham, 10 Hz tACS or 2mA tDCS. Each stimulation session will be followed by the stimulation adverse effects questionnaire.. The AHRS (*Attachment 3*) will be administered. After this the PANSS (*Attachment 5*), BACS *(Attachment 12),* CGI-S (*Attachment 8*), and SAS (*Attachment 9*) and AIMS (*Attachment 7*) data collection assessments 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.

7.4 Follow-up

One week Follow-up Visit (Visit 10, one week after last day of stimulation)
Upon participant arrival, vital signs will be taken and documented. An EEG will then be administered. The EEG recording will include resting state data along with two auditory tasks, and the EEG Questionnaire will be administered. The AHRS will then be administered to assess severity of auditory hallucinations. Each participant will be asked whether they believe their symptoms have improved (*Attachment 11*). Participants will be paid at the conclusion of this study visit.

7.5 Final Study Visit

One month Follow-up Visit (Visit 11, one month after last day of stimulation)
Upon participant arrival, vital signs will be taken and documented. An EEG will then be administered. The EEG recording will include resting state data along with two auditory tasks, and the EEG Questionnaire will be administered. The AHRS will then be administered to assess severity of auditory hallucinations, followed by the adverse events questionnaire and a review of current medications. The PANSS (*Attachment 5*), CGI-S (*Attachment 8*), and SAS (*Attachment 9*), AIMS (*Attachment 7*), and BACS *(Attachment 12)* 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.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Clinical Evaluations

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 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, the first day of stimulation, the last day of stimulation, and at the one week and one month follow up visits.

iii. 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 the initial session, first day of stimulation, the last day of stimulation and at the one month follow up visit.

iv. The Brief Assessment of Cognition in Schizophrenia (BACS) will be administered at baseline, day 5 of stimulation and at the week 5 follow-up session 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.

v. The Simpson Angus Scale (SAS) (Janno et al. 2005) is a 10 item assessment of medication related extrapyramidal side effects. The SAS will be administered at the first day of stimulation to obtain a baseline assessment, and again at day 5 of stimulation and the week 5 follow-up session to monitor symptom severity or development for each participant.

vi. The Abnormal Involuntary Movement Scale (AIMS) will be administered at the initial session to obtain a baseline assessment, and again at day 5 of stimulation and the week 5 follow-up session to monitor symptom severity or development for each participant. The AIMS is a 12 item assessment used to record the occurrence of tardive dyskinesia.

vii. The Clinical Global Impression Severity Scale (CGI-S) measures the symptom severity for patients diagnosed with mental disorders based on the clinician's total experience with that specific population. The CGI-S (Berk et al. 2008) will be administered by a clinician or trained research assistant at the initial session, the first day of stimulation, the last day of stimulation, and the week 5 follow up visit.

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 to determine ability to successfully blind using transcranial current stimulation. *(Attachment 1 and Attachment 2)*

8.2 Laboratory Evaluations

8.2.1 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 for any female participant who is unable to confirm pregnancy status. This information will be recorded on the inclusion/exclusion criteria checklist *(Appendix M)* to be completed by the researcher. Participants will also be asked to complete a drug urine test during the initial session to verify drug use status.

8.2.2 Special Assays or Procedures

The Brief Assessment of Cognition in Schizophrenia (BACS) *(Attachment 12)* will be administered during the 1st day of stimulation, the 5th day of stimulation and at the one month follow-up. 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 three treatment arms for this study (sham, 10HZ tACS or 2mA tDCS). 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 the one month follow up session. This measurement will contribute to the design of novel network-level biomarkers of schizophrenia and of treatment response.

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

9 ASSESSMENT OF SAFETY

9.1 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 a related clinical trial (IRB# 13-2995). Should there be a significant change in PANSS rating scores, (>25% increase) we will direct the participant to Dr. Cordle or Dr. Jarskog for further follow up and file a 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 B)* and an AE log *(Appendix C).*

9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1 Adverse Events

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 Report Form will be completed by the study coordinator (*Appendix B).* The AE report form includes the follow; 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, this form will be given to the PI and the Co-I who will review, comment and sign this form. Completed forms will be placed in the participant's folder.

The study coordinator will document any AE occurrence on the AE log (*Appendix C)* 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 N)* and will be filed in the participant's folder.

Relationship to Study Products: The PI and Co-I will together determine whether an AE is associated with the study treatment. The event will be labeled associated if the event is temporally related to the administration of 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.

9.2.2 Expected Adverse Reactions

Transcranial current stimulation has been used without reports of any serious side-effects. Some subjects 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. During the stimulation, the researcher will ask the participant about their comfort. Stimulation will immediately be stopped if any discomfort (more than "moderate") is reported. In theory, there is a possibility that application of weak stimulation current could induce a seizure.

These adverse reactions will be monitored with the stimulation adverse effects questionnaire (*Attachment 1 and Attachment 2)*. The following scale reflects the scoring of severity for any possible side effects.

1 = Absence of the indicated symptom
2 = Mild (awareness of a symptom but the symptom is easily tolerated)
3 = Moderate (discomfort enough to cause the researcher to be informed)
4 = Severe (incapacitating; the stimulation is terminated due to extreme discomfort)

All expected adverse reactions questionnaires are a daily source document that will be placed in each individual's folder. Should the DSMB ask to see a complete report of this information a report can be regenerated for their viewing.

9.2.3 Serious Adverse Events

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

All SAEs will be recorded on the Serious Adverse Events Form (*Appendix D)*, 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 E*) 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.

9.2.4 Unanticipated Problems.

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

The Office for Human Research Protections 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. *Please see Appendix F for an example of the Consent Amendment Tracking log.* 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.

9.3 Reporting Procedures

We will be adopting the follow table for reporting procedures:

What Event is Reported	When is Event Reported	By Whom is Event Reported	To Whom is Event Reported
Fatal or life-threatening unexpected, suspected serious adverse reactions	Within **24 hours** of initial receipt of information	Investigator	● Local/internal IRBs, DSMB
Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions	Within **48 hours** of initial receipt of information	Study Coordinator	● Local/internal IRBs/Institutional Officials, DSMB
Unanticipated adverse device effects	Within **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

9.3.1 Reporting of Pregnancy

Pregnancy tests will be administered at the initial session 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 and medical monitor.

9.4 Type and Duration of Follow-up of Participants after Adverse Events

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

9.5 Halting Rules

If a seizure occurs at the time of a study visit, a temporary hold will be placed over the study and further investigation will ensue. This could lead to stopping the study prematurely or continuing on with further safety measures in place. If two seizures are witnessed during the study visits, the entire study will be stopped prematurely. These individuals would be referred for further medical attention. It is very unlikely that a seizure will occur, given that previous studies using tDCS in

patients with depression and schizophrenia have had no seizures occur (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.

9.6 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 three arms of the study; however the specific treatment of that arm will not be disclosed. This will allow the DSMB to compare the three 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.

10 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.

10.1 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 O*) 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 4109 of the NRB. Deviations will be sent to IRB every 4-6 weeks (if necessary).

At the end of the month clinical trials meeting with the PI, 3 randomly selected informed consent forms will be chosen. The PI will verify that (1) these forms have been filled out appropriately, and (2) the consent form process described in the SOP was followed and properly documented. Should any consent form be in violation, the research team will perform and document a complete review of all consent forms.

AE and SAE are clearly defined in 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. In all weekly meetings with the PI, all AE and SAE are discussed. For our practices we have adapted the decision tree provided by UNC-CH IRB to assist with reporting of such events (*Attachment 10*).
At all weekly clinical trial team meetings, the study coordinator will chose one CRF and Source Document to asses for completion and maintenance. At weekly clinical trials meeting, with the PI will assess completeness of data on REDCap (data site). The PI has read-only access. This allows the PI to view reports that provide information on any missing data on an individual participant basis, but does not allow them to add, change or input any data.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

11.1.1 Primary Objective

Null hypothesis: There is no difference in AHRS score immediately before first stimulation session and immediately after last stimulation session between treatment groups.
Alternative hypothesis: There is a difference in AHRS score immediately before first stimulation session and immediately after last stimulation session between treatment groups.

11.1.2 Secondary Objectives

1. *Null hypothesis:* There is no difference in changes of alpha frequency power between baseline EEG and EEG at completion of stimulation between treatment groups.
   Alternative hypothesis: There is a difference in changes of alpha frequency power between baseline EEG and EEG at completion of stimulation between treatment groups.

2. *Null hypothesis:* There is no difference in PANSS score immediately before first stimulation session and immediately after last stimulation session between treatment groups.
   Alternative hypothesis: There is a difference in PANSS score immediately before first stimulation session and immediately after last stimulation session between treatment groups.

3. *Null hypothesis:* There is no difference in BACS score immediately before first stimulation session and immediately after last stimulation session between treatment groups.
   Alternative hypothesis: There is a difference in BACS score immediately before first stimulation session and immediately after last stimulation session between treatment groups.

11.2 Sample Size Considerations

This clinical trial represents a pilot study. A pilot study is a clinical trial that is conducted to decide whether a new treatment should be tested in a large controlled trial therefore we do not calculate sample size. 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 prior experience recruiting for patients with these symptoms, we expect that we can successfully recruit 48 subjects and that with 16 participants in each group that we have enough power to detect significance if there is a large effect size of twice daily tACS or tDCS on auditory hallucinations and/or the underlying biomarkers.

11.3 Final Analysis Plan

We will perform spectral analysis of resting state EEG before and after stimulation treatment and use a mixed ANOVA with the within subject factor session (immediately before first stimulation session and immediately after last stimulation session) and between subject factor treatment (sham, 10Hz tACS or 2 mA tDCS). Spectral analysis will be performed with multi-tapered estimation of the frequency spectrum followed by integration over the classical alpha EEG band (8-12 Hz). We will apply the same statistical analysis procedure for our primary outcome of AHRS, PANSS and BACS scores.

We will also use post-hoc paired or unpaired Student's t-test to identify the group or groups that differed. We will further control for multiple comparisons by using Bonferroni corrections.

12 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:

- Ensure that participant identification is on all pages of the ICF
- There is documentation that the participant is given a copy of the consent form *(Appendix G)*
- 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 N)* 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. *(Appendix J)*
- 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 N)* 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 J)* 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 and medical monitor will have access to files upon request as they will need access to the locked rooms and filing cabinets in which these documents are located. The key linking dummy identifiers with subject information will be securely destroyed after completion of data acquisition.

13 ETHICS/PROTECTION OF HUMAN PARTICIPANTS

13.1 Ethical Standard

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

13.2 Institutional Review Board

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
5. 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.

13.3 Informed Consent Process

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

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

13.4 Exclusion of Women, Minorities, and Children (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 initial session in order to determine eligibility for the study.

13.5 Participant Confidentiality

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

All data will only be referenced by dummy identifier code. Data will be stored on a password protected computer. A key connecting names and code numbers will be kept in a locked cabinet, accessible only by research personnel. All data will be stored and analyzed on password protected computers, also only accessible by research personnel. Participants will not be identified in any report or publication about this study.

13.6 Study Discontinuation

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

14 DATA HANDLING AND RECORD KEEPING

The study coordinator and research assistants are responsible for the accuracy, completeness, legibility, and timeliness of the data reported. During weekly meetings, the data will be reviewed by the PI to check for completeness and continued safety of the participants and research staff. 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.

14.1 Data Management Responsibilities

The responsibilities designated to each member of the research team are documented on the Delegation of Authority SOP (*Appendix K).* 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. Asa Cordle will be the medical monitor for the study.

14.2 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.

14.3 Types of Data

Data will be collected to determine eligibility. During the initial session, the SCID, 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 determine efficacy of treatment.

The PANSS, the CGI-S, the SAS and the AIMS will be used to collect additional data throughout the study. This questionnaire will also be administered on the 1st day of stimulation, the 5th day of stimulation, and the one week and one month follow up, in addition to during the initial session.

An EEG recording will be performed at the 1st day of stimulation, the 5th day of stimulation, and at the one week and one month follow-up. The data collected from the EEG recording will enable assessment of neurophysiological changes induced by stimulation.

14.4 Timing/Reports.

The stimulation adverse effects questionnaire will be administered at the end of each stimulation session and at each follow-up session. Any AE will be reported to the PI within 72 hours and to the medical monitor within 24 hours. Reports will be run at the end of each week and any unusual activity that could be a cause of concern will be reported to the PI at weekly meetings.

14.5 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.

14.6 Protocol Deviations

All deviations from the protocol will be addressed in study participant source documents. The researcher will complete a Protocol Deviation Log *(Appendix O)* 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.

15 PUBLICATION POLICY

This study will be registered on clinicaltrials.gov once IRB approved. There are no restrictions on publications since this is an investigator-initiated study funded by a grant agency (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.

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SUPPLEMENTS/APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

A detailed schematic describing all visits and assessments.

	STILL 2 Study Outline						
Procedures	Consent Visit	Screening Visit	Day 1 of Stimulation	Days 2 –4 of Stimulation	Day 5 of Stimulation	1 Week Follow-up	1 Month Follow-up
Signed Consent Form	X						
Vital Signs		X	X	X	X	X	X
SCID, Med Hx, Phys. Exam		X					
Incl/Excl Criteria		X					
Medications							X
AHRS	X	X	X		X	X	X
PANSS, CGI-S			X		X		X
SAS, AIMS		X			X		X
BACS			X		X		X
UDS, beta-HCG		X					
Randomization			X				
Stimulation			X	X	X		
EEG		X			X	X	X
EEG Questionnaire		X			X	X	X
Adverse Events			X	X	X		

APPENDIX B: AE REPORT FORM

Adverse Effects Report:

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

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

Research team member signature _____

Date_____

Co-Investigator :

_____

_____

_____

_____

_____

_____

Steps to be taken (if applicable)

_____

_____

_____

_____

_____

CI signature

_____Date_____

PI Comments:

_____

_____

_____
_____
_____
_____

Steps to be taken (if applicable)

_____
_____
_____
_____
_____

PI signature

_____Date_____

APPENDIX C: AE LOG

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

APPENDIX D: 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 E: 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
					☐ Yes ☐ No ☐ N/A
					☐ Yes ☐ No ☐ N/A
					☐ Yes ☐ No ☐ N/A
					☐ Yes ☐ No ☐ N/A
					☐ Yes ☐ No ☐ N/A
					☐ Yes ☐ No ☐ N/A

APPENDIX F: CONSENT AMENDMENT TRACKING LOG

Change Initiated by:		Adjustments made to consent form	Date Submitted to IRB	Date of IRB Answer	Requires Stipulations? (Y/N)	Stipulation Submission Date	IRB Approval Date
Initials	Reference ID						

APPENDIX G: INFORMED CONSENT PROCESS DOCUMENTATION

Abbreviated Study Title: _____

Participant Name: _____ Date of Birth: _____

Medical Record #: _____

Please **INITIAL** next to **"Yes" or "No"** by each line as appropriate **(if "No," an explanation MUST be provided in the notes section below).**

_____Yes _____No Participant and/or the participant's legally authorized representative (LAR) was given a copy of the consent document to read.

_____Yes _____No Ample time was provided for reading the consent document, and the participant (or participant's LAR) was encouraged to ask questions.

_____Yes _____No All questions and concerns were addressed to the satisfaction of the participant (or participant's LAR) prior to signing the consent document.

_____Yes _____No The PI or Sub-I was available for questions prior to the subject signing the consent.

_____Yes _____No The subject (or subject's LAR) agreed to participate in the study and signed/dated the consent document.

_____Yes _____No A copy of the signed consent document was provided to the participant (or participant's LAR).

❑ Verbal consent was obtained (per IRB approved consent process). Documentation of the process and the individual(s) witnessing the process is described below.

_____Yes _____No No procedures specifically related to the study were performed prior to the participant signing the consent document.

The details of this research study were discussed with the participant (or participant's LAR), including an explanation of all of the elements of the consent document. The IRB-approved consent document was signed and dated by the participant (or participant's LAR) and a copy of the signed consent document was placed in the participant's medical record (unless otherwise noted). No activities specifically related to the research were initiated until after the execution of the consent document. The principal investigator was notified of the participant's consent to be enrolled in the study and agrees with enrollment of subject.

The participant (or participant's LAR) signed consent document version _____ on _____*(date)* at _____*(time)*.

Notes:

Signature of Person Obtaining Consent | Date | Time

APPENDIX H: 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 I: IRB AMENDMENT TRACKING LOG

Change Initiated by:		Description of IRB: Type and Brief Summary	Date Submitted to IRB	Date of IRB Answer	Requires Stipulations? (Y/N)	Requires Updated Consent Form? (Y/N)	Stipulation Submission Date	IRB Approval Date
Initials	Reference ID							

APPENDIX J: DELEGATION OF AUTHORITY

Designee (full name)	Courtney Lugo	Juliann Mellin	Dr. Fred Jarskog	Dr. John Gilmore	Dr. Flavio Frohlich
Title & Position	Study Coordinator	Study Coordinator	Co-Investigator	Co-Investigator	Principal Investigator
Delegated Activity (see codes)					
Designee Signature & Dates					
Designee Initials (signed)					
	Activity Codes: 01: Informed Consent 02: Initial Session Review for Eligibility 03: Questionnaire Administration 04: CRF Entries 05: Device Administration 06: EEG Administration 07: Data Entry 08: Adverse Event Assessment 09: Adverse Event Documentation/Reporting 10: Medical Monitor				
	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 K: ENROLLMENT LOG

Subject ID		Date Consent Signed	Gender	Race	Ethnicity	Treatment Arm / Group	Explanation if subject did not complete study / Comment
1			M ☐ F ☐				
2			M ☐ F ☐				
3			M ☐ F ☐				
4			M ☐ F ☐				
5			M ☐ F ☐				
6			M ☐ F ☐				
7			M ☐ F ☐				
8			M ☐ F ☐				
9			M ☐ F ☐				
10			M ☐ F ☐				
11			M ☐ F ☐				
12			M ☐ F ☐				
13			M ☐ F ☐				
14			M ☐ F ☐				
15			M ☐ F ☐				

APPENDIX L: INCLUSION/EXCLUSION CRITERIA CHECKLIST

Inclusion Criteria		
DSM-IV diagnosis of schizophrenia, any subtype, or schizoaffective disorder, with refractory auditory hallucinations. Duration of illness >1 year.	Yes	No
18-70 years old.	Yes	No
Clinically stable for at least 12 weeks, i.e. not requiring hospitalization or a change in level of care	Yes	No
On current antipsychotic doses for approx. 4 weeks or more	Yes	No
Capacity to understand all relevant risks and potential benefits of the study (informed consent) OR has a legal guardian who can complete consent forms on the patients behalf	Yes	No

Exclusion Criteria		
Subjects with a 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 6 months	Yes	No
History of significant head injury/trauma, as defined by loss of consciousness for more than 1 hour, or recurring seizures, or requiring later cognitive rehabilitation or causing cognitive sequellae	Yes	No
Prior brain surgery	Yes	No
Any brain devices/implants, including cochlear implants and aneurysm clips	Yes	No
Co-morbid neurological condition (i.e. seizure disorder, brain tumor)	Yes	No
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	Yes	No
Non English speakers	Yes	No
Pregnancy, nursing, or if female and fertile, unwilling to use appropriate birth control measures during study participation	Yes	No

If the responses to all the inclusion criteria are YES and all the exclusion criteria are NO, the participant is able to participate in the trial.

Is the participant eligible to participate in the trial? YES NO
If NO, discontinue subject.
If YES, I have reviewed the inclusion and exclusion criteria and have determined that the participant is eligible for participation in the trial.

Investigator Signature: _____ Date: _____

APPENDIX M: NOTE TO FILE

IRB#: 14-3285 PI: Flavio Frohlich

Study Title:

_____

Date of Occurrence: _____

Research Name: _____

Participant ID: _____

Reason for Note:

_____

_____

Note:

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Corrective action (if applicable);_____

_____

_____

_____

Signature: _____ Date: _____

APPENDIX N: PROTOCOL DEVIATION LOG

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

APPENDIX O: STUDY START UP CHECKLIST

Study Start Up Checklist

Study Title: _____

Funding Source:

_____

	Date Completed	
CRMS Recorded Created	_____	
IRB Application Submitted	_____	Approved Date : _____
CVs/Certifications/Medical License	_____	
IRB Roster	_____	
IRB Statement of Compliance	_____	
PI Signature of Protocol	_____	

	Date Completed
Study Binders Created	_____
Regulatory Documents Filed	_____
Protocol Deviation Tracking Log Filed	_____
Completion of Site Training, Filed	_____
Delegation Log Completed	_____
Develop Recruitment Plan	_____
Begin Pre-Screening	_____
Source Documents Created	
Participant Folders Created	
	_____
	_____
Schedule Study Start Up Meeting	_____
Lab Kits Received	_____
Participant Supplies Received	
Investigational Device Received	

APPENDIX P: PARTICIPANT OFF STUDY FORM

Participant Initials ☐☐☐ **ID** ☐☐☐☐☐ **Date:** ☐☐ / ☐☐ / ☐☐

Month Day Year

Participant Off Study

Date participant went Off Study: ☐☐ / ☐☐ / ☐☐

Month Day Year

INDICATE OFF STUDY REASON:

- ☐ Study Activities Completed
- ☐ Side effects of study intervention (complete applicable SAE form or AE Tracking Log)
- ☐ Death
- ☐ Participant lost to follow-up* (provide comments below)
- ☐ Participant refused follow-up* (provide comments below)
- ☐ Other* (provide comments below)
- ☐ Participant withdrew (complete Early Withdrawal section below)

Was treatment unblinded? ☐[1] Yes ☐[2] No ☐[3] Not Applicable

Early Withdrawal

Last Visit Completed: ☐ *Early Withdrawal form not completed*

☐ Screening Visit	☐ Visit 3	☐ Visit 6
☐ Visit 1	☐ Visit 4	
☐ Visit 2	☐ Visit 5	☐ Visit 7

Indicate the **primary** reason the participant has withdrawn from the study (select only one):

- ☐ Participant deemed eligible but declined participation
- ☐ Participant deemed inappropriate for study participation by the PI
- ☐ Participant was determined to be ineligible after enrollment* (provide comments below)
- ☐ Identification of disease/condition after enrollment that warrants withdrawal*
- ☐ Unable to continue due to personal constraints*
- ☐ Side effects of study intervention * (complete UWI-02-007 Adverse Event Tracking Log)
- ☐ Other *

*Additional explanation required:

_____

_____

FORM COMPLETED BY: _____

APPENDIX Q: TELEPHONE LOG

Date/Time	Incoming/Outgoing	Message/Conversation	Reason for calling	Comments/Researcher Initials
	Incoming Outgoing	Message Conversation		
	Incoming Outgoing	Message Conversation		
	Incoming Outgoing	Message Conversation		
	Incoming Outgoing	Message Conversation		
	Incoming Outgoing	Message Conversation		
	Incoming Outgoing	Message Conversation		

APPENDIX R: TRAINING LOG

Title of Training:_____ **DATE:_____**

(e.g., Protocol; Amendment; IRB [include version #/date])

By signing below, each staff member verifies they have been trained on the information and understand the obligations/responsibilities associated with this training.

Training Date (if different than above)	Trainee Name (please print)	Trainee Signature	Training Format (ie Presentation; Self-Study)

Trainer Name (if relevant):_____

(Please print)

Trainer Signature (if relevant):_____

APPENDIX S: TELEPHONE RECRUITMENT SCRIPT

Hello, my name is _____. Are you contacting me in regards to the non-invasive brain stimulation study?

If 'No', redirect them as necessary)
(If 'Yes', proceed)
Do you have time now to hear about the study, answer a few screening questions, and schedule your first visit?

(If 'No', ask for a good time to call back)
(If 'Yes', proceed)

Great! This study is looking at 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 one to eight sessions, with one session being an initial information session, then five, twice daily stimulation sessions, followed by a one week then one month follow up session. The stimulation sessions need to be on consecutive days with the second session occurring 3 hours after the completion of the first session. The maximum compensation for this study is $340 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 or anticonvulsant medications? (No)
- 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)

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 an 8 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.

APPENDIX T: EEG QUESTIONNAIRE

EEG Questionnaire

Date:_____ **Participant ID:_____**

After Resting State EEG:
During this EEG task, can you tell me what you heard (if anything)?

_____

_____

_____

After Oddball task:
During this EEG task, can you tell me what you heard (if anything)?

_____

_____

_____

After click train task:
During this EEG task, can you tell me what you heard (if anything)?

_____

_____

_____