Improving Hallucinations by Targeting the rSTS with tES

NCT #: NCT05165654

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Protocol Number:	2019P001016X
Title:	Improving Hallucinations by Targeting the rSTS with tES
Design:	Double blind, sham controlled design with baseline, day 5 and 1 month follow up visits during which tES (cathodal tDCS or sham) was delivered to the right superior temporal sulcus (rSTS) from baseline to day 5 each day (5 days) twice a day for 20 mins. Participants were randomly assigned to either active cathodal tDCS or sham condition to test the effectiveness and feasibility of stimulating the rSTS using a novel targeting methodology consisting of a lesion network guided brain target linked to hallucinations.
Objectives:	Evaluate the effectiveness and safety of tDCS for improving the positive and general symptoms associated with individuals who have a history of hallucinations
Enrollment:	12 Individuals
Clinical Sites:	Beth Israel Deaconess Medical Center, Boston, MA
Patient Population:	Male or female outpatients 18-50 years of age patient's diagnosis with either schizophrenia, schizoaffective disorder, or psychotic bipolar as defined by DSM-5 or DSM-IV-TR criteria
Primary and Secondary Outcomes:	Primary Outcomes: Positive and Negative Syndrome Scale (PANSS); University of Miami Parkinson's Disease Hallucinations Questionnaire (UMPDH-Q); Auditory Hallucinations Rating Scale (AHRS). Secondary Outcomes: Global Assessment of Functioning (GAF); Young Mania Rating Scale (YMRS); Symptom Checklist 90 (SCL-90) Biological Motion; Steady State EEG (Visual, Auditory and Multimodal); Brief Assessment of Cognition (BAC); Montgomery-Asberg Depression Rating Scale (MADRS); Neurological Evaluation Scale (NES); Biological Motion.
Inclusion Criteria:	1. Meet diagnostic criteria for schizophrenia, schizoaffective disorder, or psychotic bipolar disorder as verified by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV TR) and consensus clinical diagnosis 2. had no changes to relevant anti-psychotic medications for a period of 1 month prior to participation; 3. had a sufficient level of English to allow participation. 4. 18-50 years of age In addition to the criteria above, participants for this stimulation procedure will be included if they have a history of hallucinations of any modality or experiencing moderate symptoms of hallucinations; and do not have a history of moderate-to-severe

	visual impairment secondary to glaucoma, cataract or macular degeneration.
Exclusion Criteria:	1. metal implants in head. 2. implanted electronic devices. 3. history of neurological problems, seizure or head injury. 4. skin sensitivity. 5. claustrophobia. 6. organic brain syndrome 7. intellectual disability or other cognitive dysfunction that could interfere with capacity to engage in study as determined by the PI 8. a history of substance or alcohol abuse or dependence (other than nicotine) in the last 6 months or otherwise unable to commit to refraining from alcohol use during the acute period of study participation. The acute period of study participation is defined as during their visit and 24 hours before and after their visit. 9. Significant suicidal ideation or those who have enacted suicidal behaviors within 6 months prior to intake will be excluded from study participation and referred for appropriate clinical intervention. 10. Serious medical illness or instability requiring hospitalization within the last year. 11. Experience with any cardiac event. 12. Pregnant women, lactating women, women who are breastfeeding and women of childbearing potential who are not using medically accepted forms of contraception (e.g., IUD, oral contraceptives, barrier devices, condoms and foam, or implanted progesterone rods stabilized for at least 3 months).
Statistical Methodology:	Within and between comparisons to statistically detect differences in symptoms, visual/behavioral tasks and electrophysiology measures before and after treatment conditions (cathodal tDCS and sham). To determine the effectiveness and feasibility of targeting the rSTS with a novel targeting methodology to engage target outcomes.

Statement: The design, conduct and reporting of this trial shall be conducted in accordance with the protocol, the United States 45 Code of Federal Regulations (CFR) part 46 known as "The Common Rule", 45 CFR 164.502(d), and 164.514(a)-(c) known as "The Privacy Rule" of the Health Insurance Portability and Accountability Act (HIPAA), and the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP). All Investigators will have documented

training in The Collaborative Institutional Training Initiative (CITI Program) in Biomedical Research and GCP.

Background: Functional neuroimaging studies have identified neural correlates of hallucinations across multiple brain regions. Some studies suggest a common neuroanatomical substrate independent of the sensory modality, while others suggest different neural correlates for different types of hallucinations. However, whether these neuroimaging findings represented a cause, consequence or epiphenomenon of hallucinations was unclear until recently. Using lesion network mapping, researchers demonstrated that focal brain lesions play a causal role in the development of hallucinations and can occur in different brain locations, both inside and outside sensory pathway, and that greater than 90% of lesion locations causing hallucinations are negatively connected to the right superior temporal sulcus (rSTS). The rSTS is known to play a role in social cognition, biological motion, audiovisual integration, and speech. Hence, when spontaneous activity decreases at lesion locations causing hallucinations, spontaneous activity in the rSTS increases, the exact pattern thought to predispose to hallucinations. Additionally, functional connectivity within this region is abnormal in patients with visual and auditory hallucinations. Therefore, the association between rSTS connectivity and hallucinations would suggest this region may be optimal for modulation via non-invasive brain stimulation.

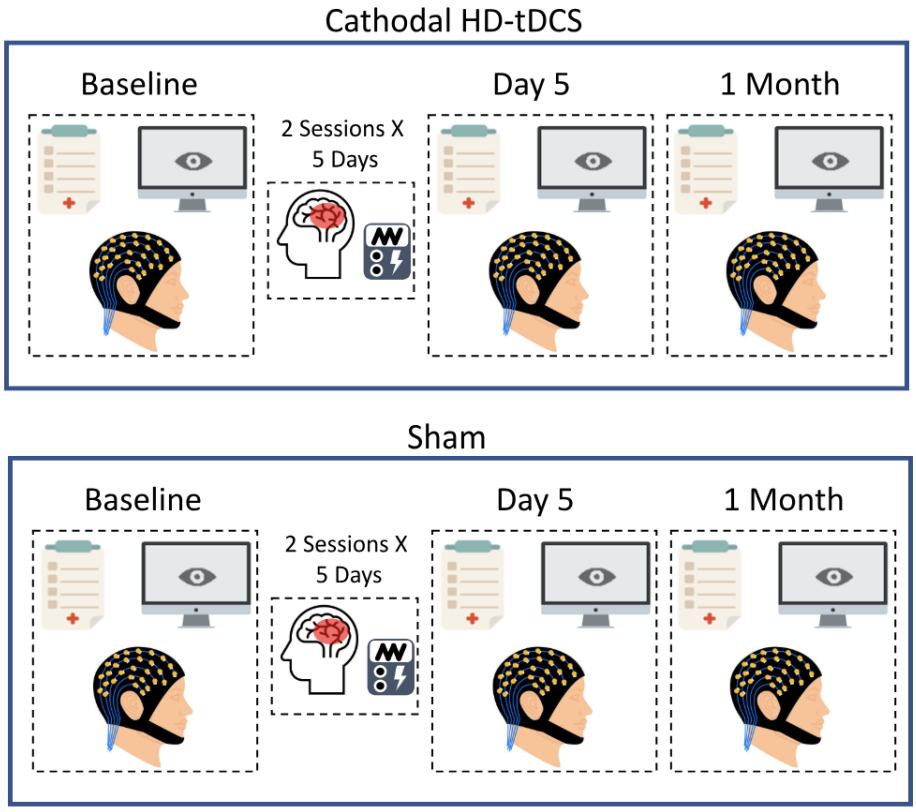
Transcranial Electrical Stimulation (tES): tES is a non-invasive brain stimulation technique which modulates cortical excitability by a weak electrical current [< 4 milliamps (mA)] between two electrodes via direct current (DC), alternating current (AC), random noise (RN) or oscillatory current (OC). This study will utilize cathodal tDCS and a sham condition. Five days of twice a day (2x20min) of tES will be used during the week.

Electroencephalography (tES): EEG is a routine, non-invasive procedure to record brain activity. EEG electrodes will be attached to the skin indirectly. Most of the electrodes are mounted in an elastic cap, which is fitted over the head and held in place with elastic straps. Some additional electrodes are placed next to the eyes, on the forehead, or behind the ears, and are held in place with adhesive collars. Electrical contact between the skin and the electrodes is achieved via a water-soluble electrode gel.

Study Rationale: Hallucinations are a core diagnostic feature of psychotic disorders. They involve different sensory modalities, including auditory, visual, olfactory, tactile, and gustatory hallucinations, among others. Hallucinations occur in multiple different neurological and psychiatric illnesses and can be refractory to existing treatments. Auditory hallucinations and visual hallucinations are found across diagnostic categories of psychotic disorders (schizophrenia, schizoaffective, bipolar disorder). Despite visual hallucinations being approximately half as frequent as auditory hallucinations, they almost always co-occur with auditory hallucinations, and are linked to a more severe psychopathological profile. Auditory and visual hallucinations at baseline also predict higher disability, risk of relapse and duration of psychosis after 1 and 2 years, especially when they occur in combination. Using a newly validated technique termed lesion network mapping, researchers demonstrated that focal brain

lesions connected to the right superior temporal sulcus (rSTS) play a causal role in the development of hallucinations. The rSTS receives convergent somatosensory, auditory, and visual inputs, and is regarded as a site for multimodal sensory integration. Here the investigators aim to answer the question whether noninvasive brain stimulation when optimally targeted to the rSTS can improve brain activity, sensory integration, and hallucinations.

Study Protocol:



Study Timeline

Study Visit Timeline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 (1-month follow up)
Consent	X					

Clinical Evaluation	X				X	X
Tasks/Cognition Testing	X				X	X
EEG	X				X	X
tES	X	X	X	X	X	
Sensation Questionnaire	X	X	X	X	X	
Self-Reports	X				X	X

Study Visits and Details:

Participants will complete baseline clinical, neuropsychological, visuoperceptual and neuro-physiological assessments (day 0), short-term follow-up (day 5) and long-term follow-up (month 1).

Pre-Screening
Subjects will be prescreened. If the subject appears to qualify for the study, they will be invited in for a screening and a baseline visit.

Screening and Baseline Procedures (approximately 3-4 hours)
Screening and baseline procedures will be conducted in the Massachusetts Mental Health Center (MMHC)/ Beth Israel Deaconess Medical Center (BIDMC) in Boston, MA. The urine toxicology screen and pregnancy test will be completed at MMHC or within BIDMC.

- Eligibility pre-screen will include a telephone pre-screening questionnaire that will assess basic inclusion and exclusion criteria.
- Eligibility screening will include a screening questionnaire that will assess more details related to inclusion and exclusion criteria and will be conducted in-person during the clinical diagnostic session (i.e., the first visit to the laboratory).
- Informed consent will be obtained
- Urine toxicology screen
- Urine pregnancy testing for females of childbearing age
  Subjects will be informed that if they do not pass the urine toxicology screen (other than prescribed medication), they will be withdrawn from the study and will not receive compensation for the initial visit. This will be made clear in the pre-screening questionnaire.
- tES screening questions for tES participation
- Demographics: Subjects will be asked to provide standard demographic information (age, sex, race/ethnicity, level of education, cohabitation status) using forms employed in previous studies.
- Psychiatric, medical, substance use history and medication review
- Signing a release to allow for access to recent psychiatric records, if confirmation of medications or psychiatric history is necessary

OBJECTIVES
Primary Objective
The primary objective of this study is to evaluate the effectiveness of tDCS for improving the positive and general symptoms associated with individuals who have a history of hallucinations (PANSS, UMPDH-Q and AHRS).

Secondary Objectives

The secondary objective of the study is to evaluate the safety and tolerability of tDCS targeting the rSTS as well as secondary clinical outcomes including depression, mania, cognition, sensory integration, electrophysiology outcomes and global functioning

Clinical and Cognitive Outcomes: Symptom ratings will be collected using the PANSS, UMPDH-Q, AHRS, YMRS, MADRS, GAF, SCL-90 and cognition with the BAC

Electrophysiology Outcomes: A steady state evoked task will be implemented probing the auditory, visual and audiovisual integration capacity of mechanisms linked to the rSTS.

Computerized behavioral tasks: The biological motion task with be used to determine the effective targeting of the rSTS and prevention of off target stimulation. Lastly, to investigate the behavioral outcomes related to visual/audio perceptual functions, the NES will be employed to determine effective auditory and visual integration abilities.

Diagnostic Assessments

Structured Clinical Interview for DSM-IV (SCID)

This is a structured clinical diagnostic screening interview for subjects 15 and older. It is used to diagnose Axis I disorders including modules on depression, mania, psychosis, alcohol and substance use, anxiety, somatic and eating disorders.

Clinical Assessments

Positive and Negative Symptom Scale (PANSS)

The ratings are based on a clinical interview conducted by trained clinical staff, covering all of the items on the rating scale.

- This rating scale is meant to capture many different types of symptoms including positive, negative, and general psychopathology symptoms. The ratings are based on a clinical interview with the participants.
- Ratings should be based on the patient's condition in the past week.
- Always use the manual with anchor points when scoring and do not try to score from your memory of the anchor points or by their headings (mild, moderate or severe).

University of Miami Parkinson's Disease Hallucinations Questionnaire (UMPDH-Q)

Administer questions on severity of hallucinations (1-6) and questions of quality of hallucinations (7-20). Each hallucination type (e.g. visual, auditory, tactile, olfactory) experienced derives an individual score. Higher total scores mean worsening symptoms.

Auditory Hallucinations Rating Scale (AHRS)

A short 7-item clinician-rated scale measuring severity, frequency, duration, loudness, impact and distress level of auditory hallucinations presently experienced. Higher total scores mean worsening symptoms.

Montgomery and Asberg Depression Rating Scale (MADRS)

Interviewer:
The questions in bold for each item ***should be asked exactly as written***. Often these questions will elicit enough information about the severity and frequency of a symptom for you to rate the item with confidence. Follow-up questions are provided; however, for use when further exploration or additional clarification of symptoms is necessary. The specified questions should be asked until you have enough information to rate the item confidently. In some cases, you may also have to add your own follow-up questions to obtain the necessary information.

Ratings should be based on the **patient's condition in the past week.*

Referent of "usual" or "normal" conditions. Several of the interview questions refer to the patient's usual or normal functioning. In some cases, such as when the patient has Dysthymia or Seasonal Affective Disorder, the referent should be to the last time they felt OK (i.e., not depressed or high) for at least a few weeks.

****Rate the highest level of psychopathology. When in doubt, rate up and record the higher score.***

Global Assessment Functioning (GAF)

Consider psychological, social, and occupational functioning on a hypothetical continuum of mental health-illness. Do not include impairment in functioning due to physical (or environmental) limitations.

Indicate appropriate code for the **LOWEST level of functioning during the week of POOREST functioning in the past month.** (Use intermediate level when appropriate, i.e., 45, 68, 72).

Young Mania Rating Scale (YMRS)

General Instructions to the Clinician:
The purpose of each item is to rate the severity of that abnormality in the patient. When several keys are given for a particular grade of severity, the presence of only one is required to qualify for that rating.

The keys provided are guides. One can ignore the keys if that is necessary to indicate severity, although this should be an exception rather than a rule.

Scoring between the points given (whole or half points) is possible and encouraged after experience with the scale is acquired; this is particularly useful when severity of a particular item in a patient does not follow the progression indicated by the keys.

Symptom Checklist 90

Self-report questionnaire for assessing psychological distress and symptoms. It consists of 90 items that measure nine primary symptom dimensions, including somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. Each item is rated on a scale from 0 (Not at all) to 4 (Extremely). The SCL-90-R also includes three global indices: Global Severity Index, Positive Symptom Distress Index, and Positive Symptoms Total.

Brief Assessment of Cognition in Schizophrenia (BACS)

Instructions (Atkins et al. 2017):

Verbal Memory (Verbal Memory & Learning Domain): *7 min*
Subjects hear a list of 15 words to remember. Words are presented by the App at a standard rate.

- Outcome measure: Total number of words recalled across 5 learning trials.

Digit Sequencing (Working Memory Domain): *5 min*
Subjects are presented with randomly ordered auditory clusters of numbers (i.e., 936) with steadily increasing trial length. Items are presented by the App at a standard rate. Subjects are asked to report the numbers in order, from lowest to highest.

- Outcome measure: Number of trials with all items in the correct order.

Token Motor Task (Motor Function): *3 min*
Subjects are presented with a virtual bowl and a supply of virtual tokens and asked to swipe a token from each side of the tablet with the index finger from each hand simultaneously and release them into the center container as rapidly as possible for 60 s.

- Outcome measure: Number of tokens correctly dragged into the container.

Semantic Fluency & Letter Fluency Tasks (Verbal Fluency Domain): *5 min*
During Semantic Fluency, subjects are given 60 s to generate as many words as possible within the category: *Animals*. Subjects are asked to generate as many words as possible beginning with a given letter. Subjects are administered two trials using letters F and S.

- Outcome measures: Total words generated for each fluency task in addition to total scores from both tasks combined to produce the Verbal Fluency domain score.

Symbol Coding (Speed of Processing): *3 min*
Subjects assign numbers to non-meaningful symbols with the use of a key that is provided. Numbers are entered on the digital keypad and appear in the location below the corresponding symbol. Following instructions and practice, subjects are given 90 s to complete as many items as possible.

- Outcome measure: Number items completed correctly within the 90 second test period.

Tower of London (Executive Functions/Reasoning and Problem Solving): *7 min*
Subjects are shown 2 images presented on opposite sides of the tablet screen. Each image shows a different configuration of 3 colored balls arranged on 3 pegs. The subject is required to accurately determine total number of times the balls in one picture would have to be moved in order to make the arrangement of balls identical to that of the other, opposing picture, while employing the standard rules employed in tower tests (balls are moved one at a time and balls on top of other balls must be moved first).

- Outcome measure: Number of correct responses.

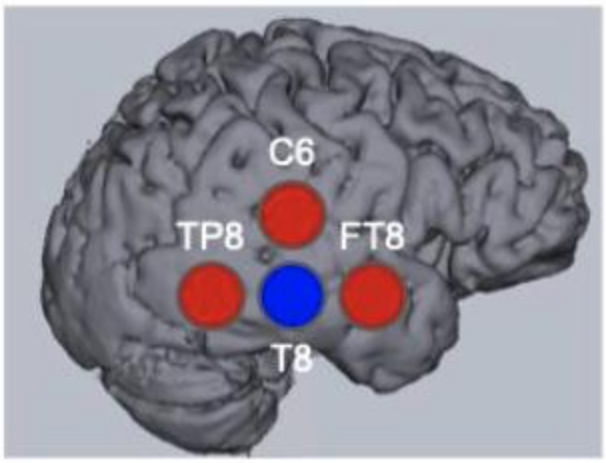
Self-Report tES Sensation Questionnaire

Given a participant after each tES session (2x20min), the questionnaire measures severity of sensations felt during the stimulation. Rated on a scale from 0 (none) to 4 (severe). In addition, the questionnaire has an open-ended question to allow participants to express any additional sensations felt during stimulation.

tDCS Montage:

Ensure to mark electrodes for stimulation and that correct settings are adjusted on tES device. A 30 second ramp should be set. All impedances should be checked before stimulation is delivered. Ensure battery life is sufficient for stimulation for the day (2x20Min stimulation). Experimenters should remain blinded.

T8 -1.5mV; TP8,
C6 & FT8 0.5mV



EEG Tasks Directions:

Resting State

For the next 5 minutes you will be asked to sit still and keep your eyes on a small white fixation cross at the center of the screen. Try to keep your eyes centered on that and try not to move excessively.

Steady State

For this last task, you will see a series of flashing black/white squares on the screen that will look like a strobe effect. They will appear in the center, left, right, or both sides of the screen but please try to keep your eyes focused on the plus sign in the center of the screen. You will also hear sounds during the task. Sometimes these sounds are played alone and other times they are played during the visual flashing.

Visual and Integration Assessments:

Three visual assessments will be conducted for all participants: Biological motion and NES. These tests are run via **MATLAB.**

Set-Up:

Bio_Motion

1. Connect Mac
    a. Black thick wire *(taped and marked "TDCS")* with Mac adaptor
2. Move the head and chin rest to be ***75 cm from the monitor*** *(marked with tape on the floor)*
3. Attach keyboard to computer and place on desk
4. Use alcohol wipe to clean:
    a. Forehead and chin rest
    b. Keyboard
5. Open up **"Visual Assessment Instructions"** PowerPoint
    a. You will use this to describe the tasks to the participant
6. Open up **"MATLAB"**
    a. Load in **"walker_nonoise_task.m"** and **"biomotionwalkerwithnoise.m"**

NES

1. .Open up **"MATLAB"**
    b. Load in **"NES.m"**
2. Open up **"Visual Assessment Instructions"** PowerPoint
    a. You will use this to describe the tasks to the participant

DATABASE Quality Assurance and Analysis

The clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures.

Description of Study Endpoints

Primary Endpoint

Change from baseline to day 5 and 1 month in clinical measures (PANSS, UMPDHQ and AHRS) total score after 1 week of tES.

Secondary Endpoints

Change from baseline to day 5 and 1 month in GAF total score after 1 week of tES. Change from baseline to day 5 and 1 month in MADRS, YMRS, SCL-90, SCL-90 after 1 week of tES. Change from baseline to day 5 and 1 month in voltage for auditory, visual and audiovisual integration steady state measures after 1 week of tES. Change from baseline to day 5 and 1 month in cognition scores after 1 week of tES.

Safety and Tolerability Endpoint

A self-rated questionnaire related to sensations of tES is given to participants after each stimulation.

General Statistical Considerations

All collected study data will be collected on Redcap and processed using R and Matlab software. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be calculated by treatment group and sham group for continuous variables.

Primary Analyses

Primary Analysis of the primary, secondary, and additional efficacy endpoints:

Mixed Model Repeated Measures analysis (MMRM)/non- parametric methods will be used to compare using within group differences as well as to determine the difference between the two treatment groups on the primary, secondary and safety endpoints depending on the distribution of the data.