Feasibility Electrical Stimulation Study for Visual Hallucinations

NCT #: NCT04870710

January 2nd, 2022

Protocol Number:	2019P001016
Title:	Feasibility Electrical Stimulation Study for Visual Hallucinations
Design:	Open Label, Non-randomized, Crossover Design with Baseline, Day 5 and 1 Month follow up visits during which tES (Cathodal tDCS & 2hz tACS) were delivered to the visual cortex from Baseline to Day 5 each day (5 days) twice a day for 20mins. Participants first entered the cathodal tDCS condition first and then after a washout period (~2 weeks) entered the 2hz tACS condition to test the effectiveness and feasibility of stimulating the visual cortex using a novel targeting methodology consisting of a lesion network guided brain target near V5/MT.
Objectives:	
Enrollment:	10 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: Steady-State Visual Evoked Potentials (SSVEP); Positive and Negative Syndrome Scale (PANSS); Biological Motion Secondary Outcomes: Global Assessment of Functioning (GAF); Velocity Discrimination; International Affective Picture System (IAPS) Task; Montgomery-Asberg Depression Rating Scale (MADRS)
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 VH or experiencing moderate symptoms of VH; had no changes to relevant anti-psychotic medications for a period of 1 month prior to participation; and do not have a history of moderate-to-severe visual impairment secondary to glaucoma, cataract or macular degeneration. Additionally, individuals will need to score above 20 on the Mini Mental Status Examine to be included in the study.
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 determine 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 next 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 statistical detect differences in symptoms, visual tasks and electrophysiology measures before and after treatment conditions (cathodal tDCS and 2hz tACS). To determine the effectiveness and feasibility of targeting the visual cortex 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.

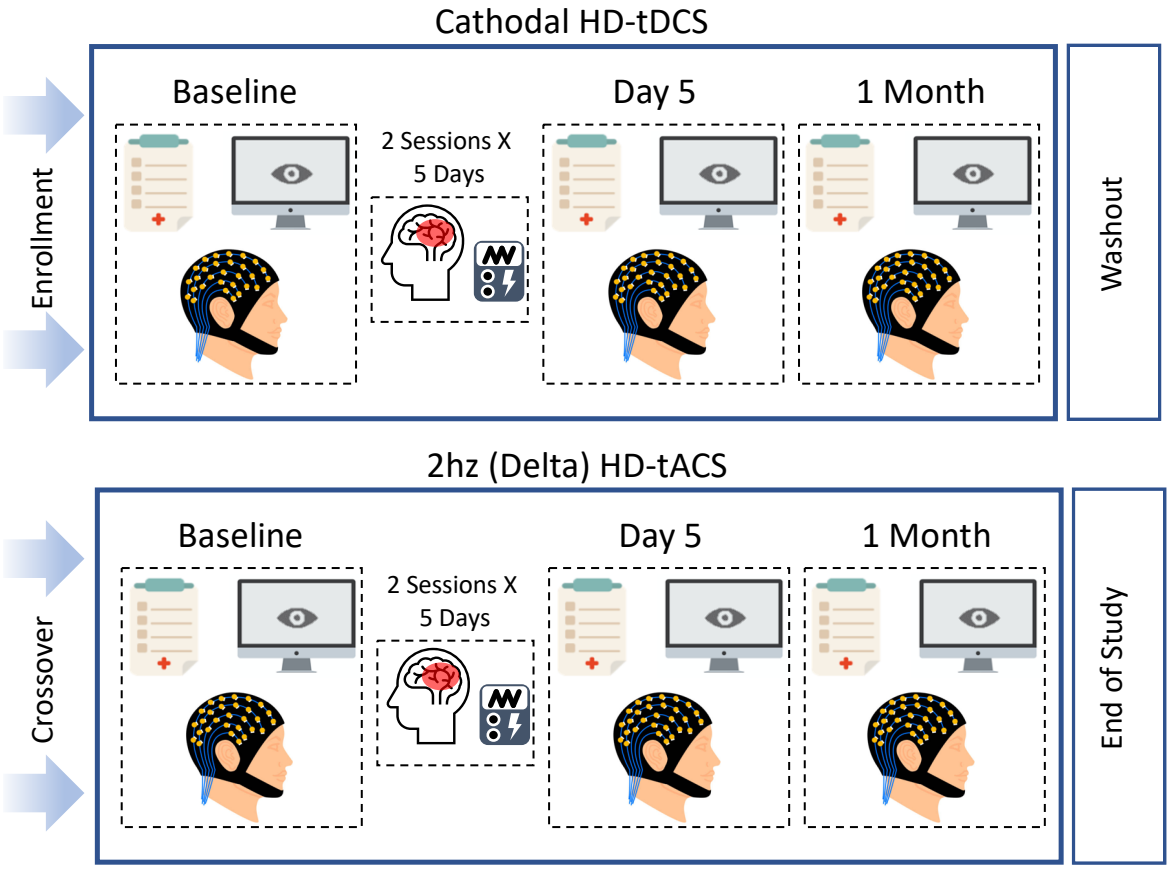
Background: Functional neuroimaging studies have identified neural correlates of VH across multiple brain regions and support hypotheses that increased visual cortex activity and sensory cortex over-stimulation generate VH (Zmigrod et al., 2016, Manford et al., 1998, Allen et al., 2008, Ffytche et al 2008). Using lesion network mapping, researchers found that the extrastriate visual cortex was causal linked to the development of (Kim et al., 2019). The association between extrastriate visual cortex activation and VH would suggest this region may be optimal for modulation via brain stimulation. While tDCS is a promising adjunctive treatment of auditory hallucinations and negative symptoms in schizophrenia, less is known about its role in treating VH. To date, two cases have been described where cathodal tDCS over the occipital area was applied to patients experiencing treatment refractory VH, and this resulted in symptomatic improvement (Shiozawa et al., 2013, Koops et al., 2017).

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 utlize cathodal tDCS and 2hz tACS. Five day of twiice a day tES will be

Electroencephalography (tES): EEG is a routine, non-invasive procedure to record brain acivity. 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: The visual system is an important site of pathology in patients with schizophrenia, schizoaffective disorder, bipolar disorder, Parkinson's disease, Lewy body dementia, Charles Bonnet syndrome, and brain lesions experiencing visual hallucinations. Visual symptoms are associated with worse poorer outcome and treatment refractoriness. A recent study identified a causal location in the extrastriate visual cortex with visual hallucinations (VH). Two case studies have found that transcranial electrical stimulation of the occipital cortex improved VH in treatment refractory patients with visual hallucinations. While promising it is unclear whether the symptom reductions resulted from activity changes in the visual cortex or not. Here we aim to answer the question whether high definition transcranial direct current stimulation when optimally targeted to a specific brain region (extrastriate visual cortex) can engage the target and improve behavioral symptoms.

Study Protocol:



Study Timeline

	Baseline	Day 2	Day 3	Day 4	Day 5	1-Month
EEG (IAPS, SSVEP)	X				X	X
Clinical Assessments	X				X	X
Questionnaires	X				X	X
Visual Tasks	X				X	X
Cognition	X				X	X
tES Treatment	X	X	X	X	X	
Sensation Questionnaire	X	X	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 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 Boston. The urine toxicology screen and pregnancy test will be completed at MMHC or within Beth Israel Deaconess Boston.

- Eligibility pre-screen will include a telephone pre-screening questionnaire that will assess basic inclusion and exclusion criteria.
- Eligibility screen 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
- If subjects have previously had a structural MRI performed through BSNIP2, they will be asked for permission to review these scans for use in neuronavigation.

OBJECTIVES

Primary Objective

The primary objective of this study is to evaluate the effectiveness of tES (cathodal tDCS and 2hz tACS) improving the positive symptoms and negative symptoms associated with psychosis along with electrophysiology outcomes and motion perception.

Secondary Objectives

The secondary objective of the study is to evaluate the safety and tolerability of tES as well as secondary clinical outcomes including depression and global functioning and other visual domains.

Clinical Outcomes: Symptom ratings will be collected using the Montgomery-Asberg Depression Rating Scale, Global Assessment of Functioning, Positive and Negative Syndrome Scale

Electrophysiology Outcomes: To probe the oscillatory capacity of the visual cortex (i.e., visual sensory integration), a steady state visual evoked potentials (ssVEP) task will be implemented. Addiotnally, participants will be asked to perform an emotional response VEP using the International Affective Picture System (IAPS).

Computerized visuoperceptual tasks: The following visual perceptual functions will be evaluated: visuospatial working memory, velocity discrimination, biological motion

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.

This will also be used when possible to confirm the diagnosis of schizophrenia in the first degree family member for the familial high risk group. Interview with a knowledgeable family member or copy of medical record is also acceptable to confirm the diagnosis.

It is possible that a potential participant is referred to this study from one of our other studies. In this case, if a previous diagnostic interview was done using the SCID then the clinician should obtain a BIDMC Release of Medical Information between the SPARCS study and the other study so the original SCID can be used as long it is updated. Be sure to check with the original study for the authorization dates to be used on the release (from the start of their participation in that study until study completion) so the correct dates are added to the release of information form. Depending on the length of time since the original SCID modules should be updated as needed. If longer than a month since the original SCID then the following updates should be done for:

1. Major depressive and manic symptoms in the past 30 days in the affective module A.
2. Inquire if there have been other mood episodes since the last SCID and determine if there has now been a past “worst” episode of depression or mania; if so evaluate past affective episodes.
3. Inquire if there has been a change in psychotic symptoms since the last SCID.
4. Inquire about current alcohol and substance use and evaluate for abuse or dependence if needed.
5. Inquire if there have been any changes in the anxiety, PTSD, somatic or eating disorders modules.

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 in 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 participant.
- All items are completed for 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).

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 necessary information.

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

Referent of "usual" or "normal" condition. 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.

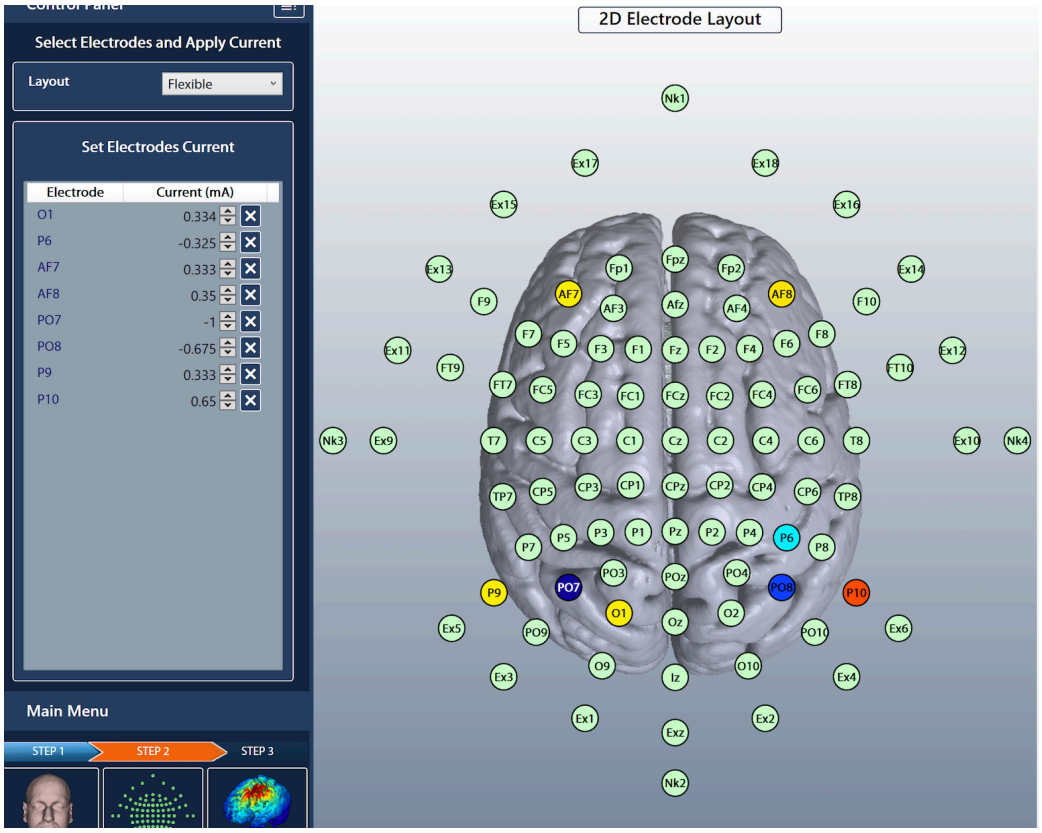
Indicate appropriate code for the **LOWEST level of functioning during the week of POOREST functioning in past month.** (Use intermediate level when appropriate, i.e., 45, 68, 72).

Visual Hallucinations Montages:

Ensure to mark electrodes for stimulation and that correct settings are adjusted on tES device.

tDCS Montage:

Active Stimulation:



tACS Montage:

Active Stimulation: tACS montage is the same montage as above. In the case of running a tACS participant, PO7, P6, P08 and AF7, AF8, P9, O1, P10 amps are the same. Frequency set to 2hz.

EEG Tasks Directions:

IAPS

For the next 12 minutes you will be presented with a series of 1-second photographs, which will show pleasant, unpleasant and neutral scenes. Some of the pictures may make you feel uncomfortable so if at any point you want to stop please let me know. There will be a red dot at the center of each picture, so try to keep your eyes centered on that.

Visual Steady State

For this last task, you will see a series of flashing red/white squares and 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. Every time you see the red/white squares, press the number 1 and you won't press anything when you see the black and white squares. This will last for 16 minutes with a break in between.

IAPS Survey

This is a survey about the pictures that you saw earlier and we want you rate each picture on 2 scales. The first scale is pleasantness, 1 is happy and 9 is unhappy and the second scale is arousal, 1 is stimulated and 9 is bored. There are 60 pictures and please use your best judgment. Do you have any questions?

Visual Assessments

Three visual assessments will be undergone for all participants: visual working memory, biological motion and speed discrimination. These tests are run via **MATLAB and Eclipse IPE**, respectively

Set-Up:

1. Connect Mac Mini to eye-tracking computer
   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 **"Eclipse IPE"**
   a. Load in **"speedDiscriminationnoClut.java"** and **"oddOneOut.java"**
7. Open up **"MATLAB"**
   a. Load in **"walker_nonoise_task.m"** and **"biomotionwalkerwithnoise.m"**

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 in Positive and Negative Syndrome Scale (PANSS) total score after 1 week of tES. Change from baseline in SSVEP voltage after 1 week of tES. Change from baseline in Biological Motion task total score after 1 week of tES.

Secondary Endpoints

Change from baseline in GAF total score after 1 week of tES. Change from baseline in MADRS voltage after 1 week of tES. Change from baseline in velocity discrimination and visuospatial working memory task total score after 1 week of tES.

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 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 endpoint depending on the distribution of the data.