

New York State Psychiatric Institute
Institutional Review Board

November 16, 2018

To: Dr. Daniel Javitt
From: Dr. Edward Nunes, Co-Chair
Dr. Agnes Whitaker, Co-Chair
Subject: Approval Notice: Continuation Expedited per 45CFR46.110(b)(1)(f)Category 8(c)

Your protocol #6662 entitled: **TDCS FOR AUDITORY HALLUCINATIONS IN SCHIZOPHRENIA** Protocol version date 11/16/2018 has been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **December 17, 2018 to December 16, 2019.**

Consent requirements:

- Not applicable: Data Analysis Only
- 45CFR46.116 (d) waiver of consent for secondary data analysis
- Signature by the person(s) obtaining consent is required to document the consent process
- Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: No Yes

Field Monitoring Requirements: Routine Special: _____

- Only copies of consent documents that are currently approved by the IRB may be used to obtain consent for participation in this study.
- A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.
- Changes to this research may not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.
- All serious and/or unanticipated problems or events involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at <http://irb.nyspi.org> for Adverse Event Reporting Procedures and additional reporting requirements.

EN/AW/kpz4alw

Signed copy on file at IRB

v. 11/15/13



Protocol Title:
tDCS for Auditory Hallucinations in Schizophrenia

Version Date:
11/16/2018

Protocol Number:
6662

First Approval:
03/04/2013

Clinic:
Brain and Behavior Clinic

Expiration Date:
12/16/2019

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Research Chief:
Daniel Javitt, MD, PHD

Cover Sheet

Choose **ONE** option from the following that is applicable to your study

If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.

I am submitting an annual continuation without modifications

Division & Personnel

Division

What Division/Department does the PI belong to?

Experimental Therapeutics/Psychiatry

Within the division/department, what Center or group are you affiliated with, if any?

Silvio O. Conte Center for Schizophrenia Research

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.



Oded Meiron, Ph.D.

Application for Continuation of Research

Status

Current Status of Study:

All research interventions were completed. Only data analysis is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.

Study has been completed. Data analysis continues for an R61-R33 application. A manuscript has been submitted to Biological Psychiatry and will be presented at ACNP 2018.

Funding

Have there been any changes in funding status since the prior approval?

No

Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?

Yes

Summary

Have there been any study findings, recent literature, or untoward events occurring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?

No

Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occurred in the past year)?

No

Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?

No

Is the study covered by a certificate of confidentiality?

Yes

Certificate expiration date (mm/dd/yyyy)

12/31/2021

Overall Progress



Approved sample size

120

Total number of participants enrolled to date

75

Number of participants who have completed the study to date

56

Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?

No

Comments / additional information

Study enrollment is ended.

Sample Demographics

Specify population

schizophrenia

Total number of participants enrolled from this population to date

65

Gender, Racial and Ethnic Breakdown

Caucasian: 26

African-American: 36

Hispanic: 9

Asian: 1

Other: 3

Male: 56

Female: 19

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year

0

Did the investigator withdraw participants from the study?

No

Did participants decide to discontinue study involvement?

No

Procedures



To create the protocol summary form, first indicate if this research will include any of the following procedures

- ✓ Psychiatric Assessment
- ✓ Neuropsychological Evaluation
- ✓ Collection of Biological Specimens
- ✓ Use of Placebo or Sham Treatment
- ✓ MRI
- ✓ Use of Investigational Drug or Device

Population

Indicate which of the following populations will be included in this research

- ✓ Adults who may have impaired decision-making ability
- ✓ Medically and Psychiatrically Healthy Subjects
- ✓ Adults
- ✓ Adults over 50
- ✓ Individuals with Psychosis

Research Support/Funding

Will an existing internal account be used to support the project?

No

Is the project externally funded or is external funding planned?

Yes

Select the number of external sources of funding that will be applicable to this study

2

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?

Yes

Select one of the following

The grant/contract is currently funded

Source of Funding

Foundation

Sponsor

Stanley Medical Research Institute (SMRI)

Select one of the following

Multicenter(NYSPI is the lead site)

Business Office

CU

Does the grant/contract involve a subcontract?



No

Funding Source #2

Is the PI of the grant/contract the same as the PI of the IRB protocol?

Yes

Select one of the following

The grant/contract is currently funded

Source of Funding

Federal

Institute/Agency

NIMH

Grant Name

Columbia Conte Center

Grant Number

P50 MH086385

Select one of the following

Multicenter(NYSPI is the lead site)

Business Office

CU

Does the grant/contract involve a subcontract?

No

Study Location

Indicate if the research is/will be conducted at any of the following

✓ NYSPI

This protocol describes research conducted by the PI at other facilities/locations

No

Lay Summary of Proposed Research

Lay Summary of Proposed Research

The purpose of the present research is to test a potential new treatment for auditory verbal hallucinations in schizophrenia that uses transcranial Direct Current Stimulation (tDCS), a neurostimulation technique that passes an extremely weak electric current through the brain. During the treatment, two electrodes are positioned on the scalp above regions of the brain implicated in abnormal cortical activity associated with auditory verbal hallucinations in schizophrenia (1-3). Due to the directional flow of current, one electrode, termed “cathodal”, inhibits cortical activity, and the other, termed “anodal”, increases cortical activity. These electrodes will be placed such that cathodal stimulation is applied to an area associated with hyperactivity and anodal stimulation to an area associated with hypoactivity. One preliminary study has



revealed that this form of neurostimulation can alleviate auditory verbal hallucination symptoms both immediately following five days of treatment and up to three months after the final treatment(4). The goal of this study is to replicate these effects and explore the mechanisms that may underpin them.

45 patients with persistent auditory verbal hallucinations will be recruited to this study. Each individual will participate in behavioral assessments lasting up to 3 hours each and will then be randomized to receive a series of active vs. sham tDCS treatments. For active treatment, patients will have the inhibitory (cathodal) tDCS electrode placed over left auditory cortex relative to an anodal placed over frontal cortex on the right side. tDCS treatments will take place for 20 min per day for 5 consecutive days. For sham, procedures will be similar except that sham (inactive) tDCS treatment will be used. Assessment batteries will then be repeated following completion of treatment and at 1 and 3 mo following treatment. In addition, patients will be offered the possibility to participate in a concurrent magnetic resonance imaging (MRI) study aimed at evaluating the effects of tDCS on activation of auditory cortex during a auditory discrimination task as well as on other imaging parameters related to resting brain activity and metabolism. Patients who agree to participate in this MRI study will be scanned before and after active or sham tDCS.

In addition to hallucinating patients, we will recruit up to 20 healthy controls and 20 non-hallucinating patients, who will have similar assessments to the patients, but will not receive tDCS. Overall, we hypothesize that tDCS treatment will lead to reduction in hallucinations, improvement in auditory function, and change in MRI measurements so that patients more closely resemble healthy volunteers and non-hallucinating patients.

Background, Significance and Rationale

Background, Significance and Rationale

The term “hallucination” refers to a sensory experience that is not in accordance with reality. For example, many individuals who suffer from schizophrenia have the experience that people are speaking to them (“auditory verbal hallucinations”) even when this is not, in fact, the case. Moreover, the voices experienced by these individuals often include derogatory content, leading to significant emotional distress. In the worst case, hallucinations may “command” individuals to perform acts that are harmful to themselves or others. In some cases, voices are perceived coming from inside the head, although in others they are experienced as coming from outside. Although hallucinations respond adequately to antipsychotic medications in most patients with schizophrenia, for some patients the hallucinations persist and remain a significant source of distress. The present project is directed toward development of a new treatment for persistent auditory verbal hallucinations in individual with schizophrenia.

One theory regarding the etiology of auditory hallucinations is that they reflect overactivity of the auditory region of brain (auditory cortex), especially left temporo-parietal cortex(1), and hypoactivity in the prefrontal cortex, especially dorsolateral and anterior cingulate regions(2, 5). In individuals with persistent hallucinations, these abnormalities persist despite treatment with antipsychotic medication. Transcranial Direct Current Stimulation (tDCS) is a relatively new technique in which small electrodes are placed over specific regions of the scalp and extremely low currents (1-2 mA) are applied to specific brain regions for up to 20 minutes. Depending upon the direction of current flow, these currents may either increase



(stimulate) or decrease (inhibit) activity in underlying brain regions. It has been reported that applying inhibitory currents over left auditory regions for 20 min per day over 5 consecutive days leads to significant, long-lasting reductions in auditory hallucinations (6). The present study seeks to replicate this finding and will utilize MRI measures of brain activity and metabolism and behavioral assessments to understand the underlying mechanisms.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

The aim of this study is to evaluate the effects on schizophrenia symptoms of tDCS applied with cathodal (inhibitory) electrode over the left temporo-parietal junction and anodal (excitatory) electrode over the left dorsolateral prefrontal cortex.

Our specific hypotheses are:

1. In comparison to sham, active tDCS treatment will decrease the severity of refractory auditory hallucinations in patients with schizophrenia
2. In comparison to sham, active tDCS treatment will decrease the severity of negative schizophrenia symptoms
3. In comparison to sham, active tDCS treatment will normalize auditory function as reflected in stronger prediction error signals in the auditory cortex during the auditory discrimination task and decreased baseline activity in this region.
4. In comparison to sham, active tDCS treatment will normalize auditory function as reflected in reduced cerebral blood flow in auditory cortex and normalized metabolism.
5. Symptom alleviation following active tDCS treatment will be maintained over the course of 3 months

The two control groups (AVH- and healthy controls) will serve as comparison groups for specific AIM 3 and 4 only.

Description of Subject Population

Sample #1

Specify subject population

Schizophrenia patients with auditory hallucinations

Number of completers required to accomplish study aims

60

Projected number of subjects who will be enrolled to obtain required number of completers



75

Age range of subject population

18-55

Sample #2

Specify subject population

Schizophrenia patients without auditory hallucinations

Number of completers required to accomplish study aims

20

Projected number of subjects who will be enrolled to obtain required number of completers

30

Age range of subject population

18-55

Sample #3

Specify subject population

Non-clinical control participants

Number of completers required to accomplish study aims

20

Projected number of subjects who will be enrolled to obtain required number of completers

30

Age range of subject population

18-55

Gender, Racial and Ethnic Breakdown

Expected racial breakdown is approximately 50% Caucasian, 16% African-American, 16% Hispanic, 16% Asian, and 2% other. Expected gender ratio is 50% male and 50% female.

Description of subject population

60 patients between the ages of 18 and 55 with a SCID diagnosis of schizophrenia or schizoaffective disorder will be enrolled in the study. All participants will exhibit refractory auditory verbal hallucinations, defined as the persistence of daily hallucinations without remission despite antipsychotic medication at adequate dosage for at least 3 months.

In addition to the primary intervention group, two comparison groups will be studied:

1. A group of patients with minimal or no auditory hallucinations (AH-) (n=20); and
2. A group of non-clinical healthy volunteers (n=20)

These subjects will be tested using a subset of the baseline assessment battery used with AH+ patients, but will not receive tDCS or repeat assessments.

All patients will be receiving antipsychotic medication at the time of study entry. Patients will remain on their present dose of antipsychotic medication throughout the treatment interval.

All participants will receive a physical examination and medical history evaluation in order to rule out disorders that might increase risks associated with tDCS, a urine toxicology screen to rule out illicit drug abuse, and a pregnancy test for women of childbearing capacity. After passing all screening criteria, participants may be removed from the study if they do not comply with study procedures, if there is a



change in their medical status, or if an adverse event has occurred.

Recruitment Procedures

Describe settings where recruitment will occur

Patients with schizophrenia will be recruited through the Lieber Schizophrenia Research Clinic and the community by our staff, all of whom will have undergone CITI and HIPAA training. Healthy controls will be recruited from the community.

How and by whom will subjects be approached and/or recruited?

Patients will be recruited from the Lieber Schizophrenia Research Clinic as follows:

1. Clinical psychiatrists and psychologists of each service will be informed about the study.
2. The clinic psychiatrist will ask patients that they feel are clinically appropriate to see if he or she would agree to be contacted about this research protocol.
3. If the patient agrees, then a study psychiatrist or psychologist would meet with the patient to describe the study and ask if the patient would be interested in participating.
4. If the patient is interested in the study and appears to meet general eligibility criteria, the patient would be evaluated for capacity to give informed consent, and if they have adequate capacity, then provide written informed consent.

Control subjects and patients from the community will be approached after they answer advertisements.

How will the study be advertised/publicized?

The study will be publicized to patients with schizophrenia via contact with the Lieber Schizophrenia Research clinic. Non-clinical control participants will be recruited by word of mouth, fliers, through our division's website and Craigslist. Advertisements will be submitted to the IRB prior to initiation of studies.

Do you have ads/recruitment material requiring review at this time?

No

Does this study involve a clinical trial?

Yes

Please provide the NCT Registration Number

NCT01898299

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?

Yes



Describe concurrent research involvement

**#4158 Lieber Schizophrenia Research Clinic (LSRC) Umbrella Protocol
6691: MOSAIC: The Management Of Schizophrenia In Clinical Practice**

Inclusion/Exclusion Criteria

Name the subject group/sub sample

Schizophrenia patients with auditory hallucinations

Create or insert table to describe the inclusion criteria and methods to ascertain them

Criterion	Method of Ascertainment
1. Age between 18-55	Self report
2. SCID primary diagnosis of DSM-IV schizophrenia or schizoaffective disorder	SCID
3. Persistent auditory verbal hallucinations	Auditory Hallucinations Rating Scale mean item score >2 and stable mean score >2 or within 25% of screening score at baseline
4. Right handed	Edinburgh Handedness Questionnaire
5. Stable antipsychotic medication for >4 weeks	Physician evaluation/Psychiatric history
6. Normal hearing	Physician evaluation
7. If female and not infertile, must agree to use one of the following forms of contraception for the duration of study participation: systemic hormonal treatment, an IUD which was implanted at least 2 months prior to screening, or "double-barrier" contraception.	Physician evaluation
8. Willing/capacity to provide informed consent	Physician evaluation

Create or insert table to describe the exclusion criteria and methods to ascertain them

Criterion	Method of Ascertainment
-----------	-------------------------



- | | |
|--|--------------------------------------|
| 1. Substance dependence or abuse (excluding nicotine) in the past 90 days | Physician evaluation |
| 2. Current significant laboratory abnormality* | screening labs |
| 3. History of seizure, epilepsy in self or first degree relatives, stroke, brain surgery, head injury with loss of consciousness > 1 hour or clear cognitive sequelae, intracranial metal implants, known structural brain lesion, devices that may be affected by tDCS (pacemaker, medication pump, cochlear implant, implanted brain stimulator) | Physician evaluation/Medical history |
| 4. Frequent and persistent migraines | Physician evaluation/Medical history |
| 5. History of adverse reaction to neurostimulation or open skin wounds that would preclude safe placement of tDCS electrodes | Self report |
| 6. Participation in study of investigational medication/device within 4 weeks | Self report |
| 7. Current use of medications known to lower seizure threshold (Lithium, Theophylline, Tricyclic antidepressants, Bupropion >450 mg/day and Clozapine >600 mg/day, brand name and generic methylphenidate/mixed amphetamine salts) | Physician evaluation/Medical history |
| 8. If female, pregnant or breast feeding at the time of screening | Urine pregnancy test and self report |
| 9. For MRI study only: Claustrophobia or metal implants or paramagnetic objects contained within the body which may interfere with the MRI scan, as determined according to the guidelines set forth in the following reference book: "Guide to MR procedures and metallic objects" Sherlock, PhD, Lippincott-Raven press, NY 1998. | History, interview |

*Note: Clinically significant laboratory abnormality refers to patient lab results that fall significantly outside the established ranges, may be indicative of the presence of a medical condition, and are not thought to reflect an artifact or routine lab error (e.g., hemolysis). Results of laboratory tests are reviewed by the study physician prior to any treatment. Abnormal lab results of clinical significance that cannot be resolved (e.g., by repeating the test to rule out laboratory error or poor quality of the original sample) will lead to exclusion from the study. Abnormal laboratory values associated with known, chronic, stable medical conditions will not be considered exclusionary unless the condition would increase risk of study participation.



Inclusion/Exclusion Criteria #2

Name the subject group/sub sample

Schizophrenia patients without auditory hallucinations

Create or insert table to describe the inclusion criteria and methods to ascertain them

Criterion	Method of Ascertainment
1. Age between 18-55	Self report
2. SCID primary diagnosis of DSM-IV schizophrenia or schizoaffective	SCID
3. Right handed	Edinburgh Handedness Questionnaire
4. Normal hearing	Physician evaluation
5. Stable course of antipsychotic medication for >1 month	Physician evaluation/Psychiatric history
6. Use of effective method of birth control for women of childbearing capacity	Physician evaluation
7. Willing/capacity to provide informed consent	Physician evaluation
8. Signed HIPAA authorization	Physician evaluation

Create or insert table to describe the exclusion criteria and methods to ascertain them

Criteria	Method of Ascertainment
1. Current persistent auditory verbal hallucinations	Auditory Hallucinations Rating Scale mean item score >0
2. Current or past history of substance dependence (excluding nicotine)	Physician evaluation
3. Substance abuse (excluding nicotine) within last 90 days	Physician evaluation/Urine toxicology screen
4. Current diagnosis of any other Axis I disorder	SCID/Psychiatric history
5. History of seizure, epilepsy in self or first degree relatives, stroke, brain surgery, head injury, intracranial metal implants, known structural brain lesion, devices that may be affected by tDCS (pacemaker, medication pump, cochlear implant, implanted brain stimulator)	Physician evaluation/Medical history



6. Frequent and persistent migraines	Physician evaluation/Medical history
7. Participation in study of investigational medication/device within 6 weeks	Self report
8. Current use of medications known to lower seizure threshold (benzodiazepines, mood stabilizers)	Physician evaluation/Medical history
9. Pregnancy	Urine pregnancy test
10. Women who are breast-feeding	Self report
11. For MRI study only: Claustrophobia or metal implants or paramagnetic objects contained within the body which may interfere with the MRI scan, as determined according to the guidelines set forth in the following reference book: "Guide to MR procedures and metallic objects" Shellock, PhD, Lippincott-Raven press, NY 1998.	History, interview

Inclusion/Exclusion Criteria #3

Name the subject group/sub sample

Non-clinical control participants

Create or insert table to describe the inclusion criteria and methods to ascertain them

Criterion	Method of Ascertainment
1. Age between 18-55	Self report
2. Right handed	Edinburgh Handedness Questionnaire
3. Normal hearing	Physician evaluation
4. Use of effective method of birth control for women of childbearing capacity	Physician evaluation
5. Willing to provide informed consent	Physician evaluation
6. Signed HIPAA authorization	Physician evaluation

Create or insert table to describe the exclusion criteria and methods to ascertain them

Criterion	Method of Ascertainment
-----------	-------------------------



- | | |
|---|--|
| 1. Current or past history of substance dependence (excluding nicotine) | Physician evaluation |
| 2. Substance abuse (excluding nicotine) within last 90 days | Physician evaluation/Urine toxicology screen |
| 3. Current diagnosis of any Axis I disorder | SCID-NP/Psychiatric history |
| 4. History of seizure, epilepsy in self or first degree relatives, stroke brain surgery, head injury, intracranial metal implants, known structural brain lesion, devices that may be affected by tDCS (pacemaker, medication pump, cochlear implant, implanted brain stimulator) | Physician evaluation/Medical history |
| 5. Frequent or persistent migraines | Physician evaluation/Medical history |
| 6. Participation in study of investigational medication/device within 6 weeks | Self report |
| 7. Current use of medications known to lower the seizure threshold | Physician evaluation/Medical history |
| 8. Pregnancy | Urine pregnancy test |
| 9. Women who are breast-feeding | Self report |
| 10. For MRI study only: Claustrophobia or metal implants or paramagnetic objects contained within the body which may interfere with the MRI scan, as determined according to the guidelines set forth in the following reference book: "Guide to MR procedures and metallic objects" Shellock, PhD, Lippincott-Raven press, NY 1998. | History, interview |

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)

No

Waiver or alteration of consent

No

Waiver of documentation of consent



No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?

No

Describe procedures used to obtain consent during the screening process

All staff members involved in screening participants will have undergone HIPAA and CITI training. Prior to screening, potential participants will be asked whether they are willing to answer questions about their medical and psychiatric history. Screening will only proceed once consent has been given.

Describe Study Consent Procedures

Study consent will be obtained by investigators only. All investigators will have undergone HIPAA and CITI training, and will be familiar with tDCS. The investigator will explain all study procedures and associated risks prior to requesting consent. When recruiting patients with schizophrenia, an M.D. who is not affiliated with the study will ask the patient questions about the study procedures and risks in order to determine whether the patient understands the study and has the capacity to provide consent.

Indicate which of the following are employed as a part of screening or main study consent procedures

✓ Consent Form

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent

Girgis, Ragy, MD

Javitt, Daniel, MD

Kantrowitz, Joshua, MD

Type in the name(s) not found in the above list

Independent Assessment of Capacity

You have indicated that your study involves subjects who **MAY LACK** capacity to consent.

Does this study require an independent assessment of capacity?

Yes

Methods/procedures for capacity assessment

An M.D. who is unaffiliated but familiar with the study will ask potential participants who have been diagnosed with schizophrenia questions about the study procedures and associated risks in order to determine whether the patient understands the study and has the capacity to provide consent.



Study Procedures

Describe the procedures required for this study

Overview

AH + Sample

The treatment portion of this study will follow a double-blind parallel arm design in which patients, raters and investigators will be blinded with respect to condition assignment. All personnel will have undergone HIPAA and CITI training. Following a clinical evaluation to determine eligibility, patients will be assigned to either the active or the sham condition. In the active condition, patients will receive cathodal stimulation to the left temporo-parietal junction and anodal stimulation to the left dorsolateral prefrontal cortex at 2mA X 20 min in each session. In the sham condition, electrodes will be placed over the same regions, but current will be applied under a “sham” approach in which currents are initially ramped up over 30 s as in the active condition, but then immediately ramped down. Prior experience has shown that subjects do not distinguish the active and sham conditions. Patients will participate in two daily sessions of 20 minutes each for 5 consecutive weekdays. Auditory hallucinations as determined by the Auditory Hallucinations Rating Scale (AHRS) and the five dimensions of schizophrenia symptoms assessed in the Positive and Negative Syndrome Scale (PANSS) will be assessed at baseline, immediately following the final treatment, and at 1- and 3-month follow-up timepoints. AHRS will be repeated prior to first treatment session. All subjects will be assessed prior to and following initiation of 5-d treatment period using a neurophysiological battery sensitive to auditory dysfunction in schizophrenia, and neuropsychological tests of auditory and general neurocognitive impairment. The neurophysiological impact of tDCS will be assessed by MRI procedures described below at baseline and immediately following the final treatment. MRI sessions are optional for AVH+ patients.

Comparison Samples

AH- patients and non-clinical control participants will first undergo clinical evaluation to determine eligibility according to their sample’s respective inclusion/exclusion criteria before participating in a baseline assessment session. Baseline assessments for the AH- patients will include the same neurophysiological battery sensitive to auditory dysfunction, neuropsychological tests auditory and general neurocognitive impairment, MRI procedures that the AH+ patient sample receives. Non-clinical control participants will only take part in the assessment of auditory function and MRI procedure.

Evaluation

After the patient signs the informed consent form and the HIPAA authorization, he/she will undergo clinical evaluation to determine study eligibility. All participants will receive medical assessments from an MD (medical history, physical examination, urine pregnancy test and toxicology) and either the SCID (schizophrenia patients) from an RN or SCID-NP (non-clinical controls) from an MA level psychologist. All patients with schizophrenia will also undergo a psychiatric history assessment with an MD. Patients in the AH+ sample will undergo additional medical assessments including blood draw, urinalysis and ECG to ensure tDCS safety. A urine pregnancy will be done during screening and prior to the first tDCS session (on Day 1).



Assessments

Baseline assessment will consist of behavioral assessments of auditory function as described below. All assessments will be performed by a rater blind to condition assignment. Symptoms will be assessed by an MA level psychologist. Neuropsychological testing will be conducted by a trained, BA level research assistant.

Behavioral Measures

Behavioral assessments will consist of ratings scales for both AH+ and AH- patients, and a hearing test for all participants including both patients and non-clinical controls. Ratings scales will include the Positive and Negative Syndrome Scale (PANSS), Auditory Hallucinations Rating Scale (AHRS), the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) neuropsychological battery, and the Self-report Quality of Life Scale (SQLS) (7). The hearing test completed by all patients and non-clinical controls will consist of a computerized tone matching task (TMT) which will assess their ability to match tones following brief delay (8, 9)

Magnetic Resonance Imaging (MRI)

Subjects who consent for the optional MRI component will undergo MRI scanning, which includes structural 3-Tesla MRI scans and task-based fMRI scans and may include resting-state fMRI, resting-state ASL, magnetic resonance spectroscopy, and diffusion tensor imaging. None of the imaging modalities used in the study will include exogenous contrasts. Total scanning time will typically be around 2 hours and will not exceed 3 hours.

MRI scans will be performed immediately before and after the treatment period with active or sham tDCS in AVH+ patients. Comparison AVH- patients and healthy participants will also undergo MRI scanning despite not receiving tDCS. On the day of MRI scanning, subjects will be accompanied to the MRI suite at the NYSPI or Neurological Institute (depending on availability). The subject will be placed in a supine position on the camera table. Head will be positioned and a plastic head-holder will be used to decrease head movement during the scan. A bite bar (a soft but firm mouthpiece) will also be offered to the subjects to prevent excessive movement. Participants may or may not bite down on the bite bar. A new disposable cover for the bite bar will be used for every new participant. The participants will be given foam earplugs to reduce the noise of the MRI as well as a MRI-compatible hand held response pad for responding to the task (multi-button response units or mouse or a similar device). The tasks will be projected from an Insight liquid crystal display (LCD) projector zoomed to a screen inside the MR suite or viewed through dual channel binocular goggles (Silent Vision SV-2600; Avotec, Inc.). All subjects will undergo a structural MRI scan at the beginning of the session to allow for anatomical co-registration. Women will have urine pregnancy testing on each MRI scan day.

MRI Screening

Before inclusion in the MRI experiment, all subjects will be screened to ensure their eligibility for MRI scanning. The screening questionnaire includes questions regarding inclusion/exclusion criteria, including the presence of ferromagnetic implants, pubertal status, and pregnancy. Questions will be asked to determine if girls/women are post-menarche or pre-menopausal. Menarche will be defined as the onset of



menstruation, and menopause will be defined as the offset of menstruation. Females will be asked during the screening process if they are currently pregnant. Questions regarding ferromagnetic implants will determine whether or not the subject will be at any risk being in the scanner. If the subject has any metallic implants (i.e. metal heart valve, aortic clips, etc.) that are unsuitable for the scanner, the subject will not be included in our study. Inclusion and exclusion in our study will be determined by the PI and co-PIs in this study. Further screening will be done via the New York State Psychiatric Institute – Dept. of Psychiatry MRI Metal Screening Questionnaire. A 38-item questionnaire that was developed by the MRI Unit will be administered to every subject before they enter the MRI scanner. This questionnaire asks specifically about metallic implants and past experiences with metal to further ascertain any possible risks the person may incur by entering the scanner. Again, if any metallic implants are detected that are unsuitable for the scanner, the subject will not be included in our study. All precautions will be taken for the safety of the participants.

fMRI Task Description (auditory discrimination task)

Participants will perform an auditory discrimination task during the fMRI scans. This task is designed to detect activation in the auditory cortex and other language-related areas, without interference from the scanner noise, regardless whether the activation is induced by external acoustic stimulation or by internally generated or spontaneous processes. Subjects will be explained that they will hear recordings of spoken sentences through headphones at random intervals while in the scanner. Each stimulus will be presented over an otherwise silent epoch, which will be followed by a short noisy imaging acquisition period. Right when the latter finishes, they will be asked if they heard any voices immediately before the scanner noise started and they would need press a button to indicate so. They will be instructed that the content of the sentences will be explicit in some cases and they will listen to the recordings before the scanning session. Before each of the two sessions in the scanner, participants will have a training session in a computer outside of the scanner. The training session will last about 30 minutes.

Although our MRI Scans are for research purposes (and not clinical purposes), a credentialed, board-certified radiologist will perform a clinical reading for gross structural abnormalities on every MRI within 1 month of scanning. If anything clinically significant is found, Dr. Javitt will be notified immediately, and an appropriate clinical referral will be provided to the participant. In the case that an MRI technician or other member of the research team suspects that an MRI scan suggests evidence of a significant lesion, the PI will be notified immediately. If the reading yields a finding of immediate clinical concern, the radiologist will provide an oral report followed by a written note to the PI and Director of the MRI unit. A written report will be provided within two weeks of the oral report. Results of the MRI will be provided to the volunteers by a study physician. Volunteers can opt to receive a letter regarding the results of the MRI on the consent forms. Participants requesting a letter will receive one using the language provided by the IRB.

Treatment

Only patients in the AH+ sample will receive tDCS treatment. Prior to the first treatment, all female subjects will receive a pregnancy test. Stimulation will be performed using a battery-driven BrainStim SYS (Brainvision LLC, Germany), and transferred through two 7x5 cm sponge electrodes soaked in a saline solution (0.9% NaCl). In accordance with a recent tDCS study (21) showing beneficial effects of tDCS stimulation in reducing AVH in hallucinating schizophrenia patients, we will use a similar stimulation



montage. In the active tDCS condition the cathodal electrode will be placed over the left temporoparietal junction, and the anodal electrode will be placed over right DLPFC. In accordance with recent studies of tDCS in other psychiatric or neurological illnesses(22-24), the stimulation level will be set at 2 mA for 20 minutes. Stimulation sessions will be conducted twice a day on 5 consecutive weekdays. Each daily session will be separated by at least 3 hours. In sham stimulation, electrodes are located in the same positions as in active stimulation and the same fade in/fade out ramp will be applied and the constant current will last only 30 s. Small current pulses will also occur infrequently (every 550 ms, 110 mA over 15 ms) through the remainder of the 20-minute session to produce similar stimulation sensation between conditions. During the treatment sessions, subjects will be allowed to watch a silent movie or read material of their choice.

Treatments will be administered by a trained, BA-level research assistant under supervision of an MD. The RA will undergo a progression of graduating steps consisting of observation, implementation under supervision, and implementation with guidance.



Safety:

We will monitor for potential adverse events of tDCS with the Wong-Baker Faces Pain Rating Scale (WBFPRS, Figure). The WBFPRS is readily understood by patients and provides general evaluation of discomfort. Additionally, we will monitor discomfort and potential objective adverse effects of tDCS (e.g. skin redness) as suggested by "Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int J Neuropsychopharmacol.* 2011;14:1133-45: (Figure 2). Any score rated at a 3 or greater in severity will require immediate evaluation by a qualified member of the clinical team (Dr. Stefan Rowny). Both are familiar with Brain stimulation procedures.

In these cases, the psychiatrist will check in via phone with the subject the following day, and then as clinically indicated.

Additionally, subjects will receive the CGI-I scale prior to each treatment session to evaluate clinical stability. Additionally, **at baseline and after the final treatment**, patients will undergo pure tone audiometry testing for safety screening. If a change in auditory threshold is discovered, the treating physician will inform the patient and discuss whether or not to continue with treatment. Furthermore, if a change is discovered, the patient's hearing will be tested again periodically until either it returns baseline or the clinician determines that the change is permanent.

Post-treatment Assessments

Immediately following completion of last treatment, patients in the AH+ sample will have 1 tube of blood drawn for BDNF levels. Within 1 week following completion of treatment, patients will have repeat of baseline behavioral and ERP methods. Behavioral assessments will also be repeated at 1- and 3-month follow-up timepoints. Response to treatment will be defined as >15% reduction in AHRS score. **After the completion of the 3 month visit, subjects will be offered the opportunity to do one week of optional, open label active treatment using identical procedures to the blinded treatment. Subjects will be seen once after the week of open treatment for a follow-up visit**

Schedule of Events

Please see attached table.

Comparison Samples

Participants in the AH- and non-clinical control samples will take part in a baseline assessment session only. AH- patients will be assessed via the SCID, AHRS, PANSS/SQLS, MATRICS/TMT, and ERP procedure. Non-clinical control participants will be assessed via the SCID-NP procedure.

Genetics Blood draw:

Only AVH+ subjects will be asked to participate in the genetics blood draw.



tDCS is thought to work in part by stimulation of BDNF (Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, Lu B. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. *Neuron*. 2010;66:198-204. PM#2864780). Furthermore, plasma BDNF is known to correlate with CSF BDNF (Pillai A, Kale A, Joshi S, Naphade N, Raju MS, Nasrallah H, Mahadik SP. Decreased BDNF levels in CSF of drug-naive first-episode psychotic subjects: correlation with plasma BDNF and psychopathology. *Int J Neuropsychopharmacol*. 2010;13:535-9) and so represents an appropriate reflection of potential effects of tDCS on CNS plasticity. We predict that an increase in plasma BDNF may serve as a marker of "adequate" tDCS. D-serine is an endogenous modulator of NMDAR function that is known to modulate dendritic architecture in brain (Balu DT, Coyle JT. Neuronal D-serine regulates dendritic architecture in the somatosensory cortex. *Neurosci Lett*. 2012;517:77-81. PM#3400345). D-serine synthesis is dynamically regulated by compounds (e.g. nitric oxide) that also affect brain plasticity (1. Darra E, Ebner FH, Shoji K, Suzuki H, Mariotto S. Dual cross-talk between nitric oxide and D-serine in astrocytes and neurons in the brain. *Cent Nerv Syst Agents Med Chem*. 2009;9:289-94). Although there is less literature regarding effects of tDCS on D-serine regulation, nevertheless addition of this measurement (which is done by the Cooper lab) adds little expense to the study and does not require additional phlebotomy. We postulate that successful tDCS will be accompanied by increased D-serine release and possibly dendritic rearrangement in brain, and will be reflected in peripheral (plasma) D-serine concentrations.

In reviewing the literature, we note that there is also evidence that BDNF gene polymorphisms affect response to tDCS (Antal A, Chaieb L, Moliadze V, Monte-Silva K, Poreisz C, Thirugnanasambandam N, Nitsche MA, Shoukier M, Ludwig H, Paulus W. Brain-derived neurotrophic factor (BDNF) gene polymorphisms shape cortical plasticity in humans. *Brain Stimul*. 2010;3:230-7). It has also been demonstrated that individuals with common polymorphisms of the BDNF gene may show differential response to tDCS enhancement of brain plasticity. Thus, for both facilitatory tDCS (24 subjects, 10 heterozygotes) and inhibitory tDCS (19 subjects, 8 heterozygotes), carriers of the Val66Met allele displayed enhanced plasticity. In the present study, we will perform a secondary analysis to evaluate whether Val66 Met carriers show preferential response to tDCS treatment.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Treatment Termination

Study participation for patients in the AH+ sample will be terminated for subjects with a CGI-I worsening of 2 or greater for two consecutive days, or a CGI-S of 6 or 7 at anytime.



Participants in all samples may choose to terminate their involvement at any time.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens
Blood samples will be drawn for patients in the AH+ sample only. No blood or biological samples will be collected from participants in the AH- or non-clinical control samples.

12 cc at screening will be drawn for blood work-up (Chem 20, Thyroid function) to determine tDCS treatment safety.

30 cc tube of blood will be collected for D-serine and BDNF assessment and genetics (optional).

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment

SCID: 60 min

SCID-NP: 30 min

AHRS: 20 min

PANSS: 30 min

MATRICES battery (without SC): 1 hr

Tone Matching Test: 20 min

SQLS: 15 min

EEG for ERP procedures: 3 hrs

Wong-Baker Faces Pain Rating Scale 1 minute

CGI-S and CGI-I 5 minutes

Brunoni safety scale 5 minutes

Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study

✓ Device

Off label and investigational use of devices

Device #1



Name of the device

BrainStim SYS

Manufacturer and other information

Brain Vision LLC

Approval Status

IDE is approved

IDE#

CE Reg#MED30003

Who holds the IDE/IDE sponsor?

Other

Enter Name

Brain Vision LLC

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?

No

Treatment to be provided at the end of the study

None. This treatment will be added to standard-of-care treatment for persistent auditory hallucinations which consists of use of antipsychotic medications.

Clinical Treatment Alternatives

Clinical treatment alternatives

Standard-of-care treatment for persistent auditory hallucinations consists of use of antipsychotic medications.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

MRI

There are no known risks to the use of MRI per se. However, three areas of concern are addressed in the next section. The first is the safety risk posed by the attraction of ferromagnetic metal objects by high strength magnetic fields. The second is the discomfort some subjects experience during confinement within the bore of the MRI system. The third is the loud noise made by the gradients during imaging. These risks occur for all clinical MRI exams and are not increased by the proposed research. The images obtained from structural and functional scanning are automatically transferred from the scanner to a workstation that strips potentially identifying data from the image headers, writes the data as image volumes identified by study



number only, and stores the data on our password-protected server in a directory only accessible by the study investigators. All MRI studies follow guidelines set by the FDA with regard to specific absorption ratio (SAR), limits on gradient slew rate (dB/dt), and noise. Having ascertained the absence of implanted metal foreign objects using the aforementioned screening form, subjects and staff remove all other metal objects, including clothing with metal clasps, before entering the magnet room. The magnetic properties of unknown material are tested outside the magnet room with a strong permanent magnet. Participants and staff are also instructed to enter the magnet room slowly and to pause at the entrance to determine if any items on their person may be pulling toward the magnet. Participants wear insert earplugs during scanning to reduce noise levels below FDA limits. General Electric engineers have recently measured the sound levels within our scanners and have determined that it is compliant with FDA guidelines.

Some people have reported sensations during MRI scans, such as "tingling" or "twitching" (or, very rarely, a painful sensation), which are caused by changes in the magnetic field that can stimulate nerves in the body. In our experience, no one has had sensations from the MRI that did not stop when the scanning stopped. An acute risk of burns to the skin is presented by medicinal skin patches, and participants will be asked to remove patches before entering the scanner. Some participants may feel uncomfortable or confined once positioned within the bore of the MRI system and it may cause some subjects to feel anxious.

Evaluation

Patients with schizophrenia may experience some discomfort as a result of questions asked during the psychiatric evaluation, but this should be comparable to their experiences in standard care. For participants recruited for the AH+ sample who receive a blood draw: occasionally, redness or a bruise may develop at the site where blood was drawn. If this occurs, it will usually disappear in a few days. Some people become dizzy and faint when their blood is drawn.

tDCS (AH+ Sample Only)

Since the development of tDCS in the 1960's, hundreds of subjects have participated in studies and received tDCS without any adverse effects. There has been no evidence of neuronal damage induced by tDCS: in two evaluations, Nitsche and colleagues (25, 26) found no elevation of neurone-specific enolase (sensitive marker of neuronal damage). McCreery et al.,(27) demonstrated that current densities below 25mA/cm² do not induce brain tissue damage even by applying high-frequency stimulation over several hours. In our protocol, we stimulate with a maximum current density of 0.057 mA/cm², a thousand fold below this limit. Duration of stimulation is an additional factor contributing to potential tissue damage, which has been detected at a minimum total charge of 216 C/cm² (28). (Total charge=current density x stimulation duration.) This protocol exposes subjects to maximum total charges of 0.022 C/cm², which is far below the established safety threshold. Iyer et al. (29) demonstrated the safety of tDCS applied at 1mA and 2mA for 20 minutes to normal subjects and noted some enhancement of verbal fluency after 2mA of stimulation, but no adverse events. A recent study (30) has demonstrated the safety of 1mA of cathodal tDCS for 20 min in patients with refractory epilepsy. The authors concluded that tDCS does not induce seizures and may have an anti-epileptic effect. Fregni et al, in May 2006 (31), report that patients suffering from central pain secondary to traumatic spinal cord injury safely tolerated tDCS at 2mA for 5 consecutive days, 20 min daily, with significant pain improvement but no significant influence on cognitive performance before and



after treatment.

Some participants reported redness, itching, and mild scabbing of the skin under the electrodes during and after tDCS. Some subjects have reported a sunburn like sensation under the electrodes while current was turned on. This has sometimes persisted for an hour or more after the current was turned off. Mild scabbing has also been observed under an electrode, which resolved after a few days. Both of these events (sunburn like sensation and scabbing) appear to be related to drying out of the sponge electrodes, which we learned from another investigator working with tDCS. Since then we have kept the sponges sufficiently moist, and irritation has been minimal or absent, while scabbing has not recurred.

Some subjects may also experience mild nausea during or after the stimulation. In a study involving one-hundred and two subjects, 2.9% of the participants reported feeling nauseous after receiving tDCS (32).

Reported side effects of tDCS include reddening of the skin under the electrodes (reported in two subjects with recently shaved heads) and itching under the electrode sites while the current was turned on.

Genetics: there are potential dangers in releasing DNA information, such as jeopardy to insurability (risk to ability to obtain insurance), discrimination against employers, landlords and others.

Describe procedures for minimizing risks

tDCS

Routine safety procedures are in place to screen subjects prior to scanning, maintain security of the restricted access areas, and ensure that system security features are in good working order.

To minimize chemical reactions at the electrode-skin interface, non-metallic, conductive rubber electrodes, covered completely with saline-soaked sponges will be used, as recommended by Nitsche and Paulus, 2000 (33).

Electrode sponges will be kept moist in order to avoid skin irritation.

A research physician will be present at all times to monitor patient safety.

Operation of cellular (wireless) devices, telephones, or two-way radios may produce changes in device output, and thus should not be used in close proximity (< 1m).

We do not apply electrodes over broken or irritated skin.

The use of other stimulation electrodes during the treatment period will be avoided.

Lead wires are configured so that they cannot be plugged into power outlets such as wall sockets and line cord receptacles.

MRI

In order to minimize risks and discomforts to participants, we will:

- Screen for metallic devices, implants and other contraindications to scanning by using a screening questionnaire.



- Exclude pregnant subjects and conduct a urine pregnancy test prior to scanning.
- We will also exclude subjects with claustrophobia. We will reduce this potential adverse reaction by discussing the procedure prior to entry into the magnet room, by providing the subject with a mirror through which they can look out into the room, and by communicating with the subject over the intercom. If a subject continues to feel uncomfortable, the imaging procedure is terminated and the subject is removed from the magnet.
- Staff will provide adequate medical, safety monitoring and observation during scanning.
- Our staff will be available to provide support, reduce anxiety, optimize the comfort of the subject and remove the subject from the machine if requested.

Evaluation

Psychiatric evaluations will be performed by a trained clinical rater with patient experience. Blood draws will be performed by a trained phlebotomist.

Genetics: blood samples will be coded. No personal identification will link subjects with the blood sample, and the genetic information will not be made available to anyone (including the subject and their physician). We will apply for a certificate of confidentiality as an additional protection.

Methods to Protect Confidentiality

Describe methods to protect confidentiality

All data (written and electronic) will be coded by number. Personal identifying information will be sorted in an electronically secure database at New York Psychiatric Institute. A master list matching subjects with codes will be kept under lock and key, separate from any research records or the computer database, with access restricted to research staff, to the extent permitted by law. Only staff directly involved in this project will have access to the master list linking subject names to code numbers. In the informed consent form, subjects are told that the information they provide and all findings of testing will be kept strictly confidential, with access limited to the research staff, and possibly state or federal regulatory personnel. Subject data will be kept in a computer, but the subject's name will not appear in this database. The information will only be linked to a code number assigned for the purpose of maintaining privacy. Only members of the research team will have access to the computer.

Will the study be conducted under a certificate of confidentiality?

Yes, we have already received a Certificate of Confidentiality

Direct Benefits to Subjects



Direct Benefits to Subjects

Participants may experience no direct benefits from their involvement in this study. For schizophrenia patients receiving treatment, in one prior study using this procedure, a 30% reduction in hallucination severity was observed along with a significant reduction in Positive and Negative Symptoms.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?

Yes

Please describe and indicate total amount and schedule of payment(s).

Include justification for compensation amounts and indicate if there are bonus payments.

AVH+ subjects will be paid \$50 for Baseline, Post Treatment, 1 month, and 3 month visits and \$100 for 5 TDCS/EEG visits. If they complete the optional ERP sessions, they will be paid an additional 15 dollars an hour (for approximately 3 hours per session for two sessions), an additional \$20 for optional genetic/biomarker blood draws, and an additional \$200 if they complete all optional MRI procedures. Total payment will be \$1040 if they complete the entire study and the optional ERP and MRI components. Reasonable transportation costs (such as subway/bus fare or local taxi fare) will be reimbursed.

Control subjects (both patients and healthy control groups) will be paid \$15 an hour, and approximately \$90 for the entire study. They will additionally receive \$200 if they participate in the MRI study.

References

References

1. Silbersweig DA, Stern E, Frith C, Cahill C, Holmes A, Grootenck S, et al. A functional neuroanatomy of hallucinations in schizophrenia. *Nature*. 1995;378(6553):176-9. Epub 1995/11/09.
2. Lawrie SM. Reduced frontotemporal functional connectivity in schizophrenia associated with auditory hallucinations. *Biological psychiatry*. 2002;51(12):1008.
3. Sanfilippo M. Volumetric measure of the frontal and temporal lobe regions in schizophrenia: Relationship to negative symptoms. *Archives of general psychiatry*. 2000;57(5):471-80.
4. Brunelin J. Efficacy and safety of bifocal tDCS as an interventional treatment for refractory schizophrenia. *Brain stimulation*. 2011.
5. Sanfilippo M, Lafargue T, Rusinek H, Arena L, Loneragan C, Lautin A, et al. Volumetric measure of the frontal and temporal lobe regions in schizophrenia: Relationship to negative symptoms. 2000;57(5):471-80.
6. Brunelin J. Theta burst stimulation in the negative symptoms of schizophrenia and striatal dopamine release. *Schizophrenia research*. 2011;131(1-3):264-5.
7. Wilkinson G, Hesdon B, Wild D, Cookson R, Farina C, Sharma V, et al. Self-report quality of life



- measure for people with schizophrenia: the SQLS. *The British journal of psychiatry : the journal of mental science*. 2000;177:42-6. Epub 2000/08/17.
8. Leitman DI, Sehatpour P, Higgins BA, Foxe JJ, Silipo G, Javitt DC. Sensory deficits and distributed hierarchical dysfunction in schizophrenia. *The American journal of psychiatry*. 2010;167(7):818-27. Epub 2010/05/19.
9. Strous RD, Cowan N, Ritter W, Javitt DC. Auditory sensory ("echoic") memory dysfunction in schizophrenia. *The American journal of psychiatry*. 1995;152(10):1517-9. Epub 1995/10/01.
10. Javitt DC, Steinschneider M, Schroeder CE, Arezzo JC. Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*. 1996;93(21):11962-7. Epub 1996/10/15.
11. Umbricht D, Schmid L, Koller R, Vollenweider FX, Hell D, Javitt DC. Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: implications for models of cognitive deficits in schizophrenia. *Arch Gen Psychiatry*. 2000;57(12):1139-47. Epub 2000/12/15.
12. Javitt DC, Jayachandra M, Lindsley RW, Specht CM, Schroeder CE. Schizophrenia-like deficits in auditory P1 and N1 refractoriness induced by the psychomimetic agent phencyclidine (PCP). *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*. 2000;111(5):833-6. Epub 2000/05/10.
13. Roth W, Cannon E. Some features of the auditory evoked response in schizophrenics. *Arch Gen Psychiatry*. 1972;27:466-71.
14. Umbricht D, Krljes S. Mismatch negativity in schizophrenia: a meta-analysis. *Schizophr Res*. 2005;76(1):1-23. Epub 2005/06/02.
15. Friedman T, Sehatpour P, Dias E, Perrin M, Javitt DC. Differential relationships of mismatch negativity and visual p1 deficits to premorbid characteristics and functional outcome in schizophrenia. *Biological psychiatry*. 2012;71(6):521-9. Epub 2011/12/24.
16. Light GA, Swerdlow NR, Rissling AJ, Radant A, Sugar CA, Sprock J, et al. Characterization of neurophysiologic and neurocognitive biomarkers for use in genomic and clinical outcome studies of schizophrenia. *PloS one*. 2012;7(7):e39434. Epub 2012/07/18.
17. Gonzalez-Burgos G, Lewis DA. NMDA Receptor Hypofunction, Parvalbumin-Positive Neurons and Cortical Gamma Oscillations in Schizophrenia. *Schizophrenia bulletin*. 2012. Epub 2012/02/23.
18. Mulert C, Kirsch V, Pascual-Marqui R, McCarley RW, Spencer KM. Long-range synchrony of gamma oscillations and auditory hallucination symptoms in schizophrenia. *International journal of psychophysiology : official journal of the International Organization of Psychophysiology*. 2011;79(1):55-63. Epub 2010/08/18.
19. Spencer KM, Niznikiewicz MA, Nestor PG, Shenton ME, McCarley RW. Left auditory cortex gamma synchronization and auditory hallucination symptoms in schizophrenia. *BMC neuroscience*. 2009;10:85. Epub 2009/07/22.
20. Ford JM, Roach BJ, Mathalon DH. Assessing corollary discharge in humans using noninvasive neurophysiological methods. *Nature protocols*. 2010;5(6):1160-8. Epub 2010/06/12.
21. Brunelin J, Mondino M, Gassab L, Haesebaert F, Gaha L, Suaud-Chagny MF, et al. Examining Transcranial Direct-Current Stimulation (tDCS) as a Treatment for Hallucinations in Schizophrenia. *The American journal of psychiatry*. 2012. Epub 2012/05/15.
22. Nitsche MA. Treatment of depression with transcranial direct current stimulation (tDCS): a review. *Experimental neurology*. 2009;219(1):14.
23. Boggio PS, Rigonatti SP, Ribeiro RB, Myczkowski ML, Nitsche MA, Pascual-Leone A, et al. A



- randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum*. 2008;11(2):249-54. Epub 2007/06/15.
24. Brunelin J, Mondino M, Haesebaert F, Saoud M, Suaud-Chagny MF, Poulet E. Efficacy and safety of bifocal tDCS as an interventional treatment for refractory schizophrenia. *Brain Stimul*. 2012;5(3):431-2. Epub 2011/11/01.
25. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*. 2001;57(10):1899-901. Epub 2001/11/28.
26. Nitsche MA, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W. Safety criteria for transcranial direct current stimulation (tDCS) in humans. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*. 2003;114(11):2220-2; author reply 2-3. Epub 2003/10/29.
27. McCreery DB, Agnew WF, Yuen TG, Bullara L. Charge density and charge per phase as cofactors in neural injury induced by electrical stimulation. *IEEE transactions on bio-medical engineering*. 1990;37(10):996-1001. Epub 1990/10/01.
28. Yuen TG, Agnew WF, Bullara LA, Jacques S, McCreery DB. Histological evaluation of neural damage from electrical stimulation: considerations for the selection of parameters for clinical application. *Neurosurgery*. 1981;9(3):292-9. Epub 1981/09/01.
29. Iyer MB, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann EM. Safety and cognitive effect of frontal DC brain polarization in healthy individuals. *Neurology*. 2005;64(5):872-5. Epub 2005/03/09.
30. Fregni F, Thome-Souza S, Nitsche MA, Freedman SD, Valente KD, Pascual-Leone A. A controlled clinical trial of cathodal DC polarization in patients with refractory epilepsy. *Epilepsia*. 2006;47(2):335-42. Epub 2006/02/28.
31. Fregni F, Boggio PS, Lima MC, Ferreira MJ, Wagner T, Rigonatti SP, et al. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. *Pain*. 2006;122(1-2):197-209. Epub 2006/03/28.
32. Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain research bulletin*. 2007;72(4-6):208-14. Epub 2007/04/25.
33. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of physiology*. 2000;527 Pt 3:633-9. Epub 2000/09/16.

Uploads

- Upload the entire grant application(s)
- Upload copy(ies) of unbolded Consent Form(s)
- Upload copy(ies) of bolded Consent Form(s)
- Upload a copy of Certificate of Confidentiality
- Upload copy(ies) of the HIPAA form
- HIPAA revised.pdf
- Upload any additional documents that may be related to this study

New York State Psychiatric Institute (NYSPI)
Authorization to Use or Disclose Health Information during a Research Study

Protocol Number: 6662

Principal Investigator: Daniel Javitt MD, PhD

Name of Study: tDCS for Auditory Hallucinations in Schizophrenia

Before researchers can use or share any identifiable health information (“Health Information”) about you as part of the above study (the “Research”), the New York State Psychiatric Institute (NYSPI) is required to obtain your authorization. You agree to allow the following individuals and entities to use and disclose Health Information about you as described below:

- New York State Psychiatric Institute (NYSPI), your doctors and other health care providers, if any, and
- The Principal Investigator and his/her staff (together “Researchers”). Researchers may include staff of NYSPI, the New York State Office of Mental Health (OMH), Research Foundation for Mental Hygiene, Inc. (RFMH), and Columbia University (CU), provided such staff is a part of the study, and
- Providers of services for the Research at CU, NYSPI and/or RFMH, such as MRI or PET, or Central Reference Laboratories (NKI), if indicated in the consent form.

1. The Health Information that may be used and/or disclosed for this Research includes:

- All information collected during the Research as told to you in the Informed Consent Form.
- Health Information in your clinical research record which includes the results of physical exams, medical and psychiatric history, laboratory or diagnostic tests, or Health Information relating to a particular condition that is related to the Research.
- Additional information may include:

2. The Health Information listed above may be disclosed to:

- Researchers and their staff at the following organizations involved with this Research:
your treating psychiatrist
- The Sponsor of the Research,
Stanley Foundation and the NIMH
and its agents and contractors (together, “Sponsor”); and
- Representatives of regulatory and government agencies, institutional review boards, representatives of the Researchers and their institutions to the level needed to carry out their responsibilities related to the conduct of the research.
- Private laboratories and other persons and organizations that analyze your health information in connection with this study
Nathan Kline Institute
- Other (family members or significant others, study buddies, outside agencies etc.) Specify:

3. By giving permission to release your Health Information as described above, you understand that your Health Information may be disclosed to individuals or entities which are not required to comply with the federal and state privacy laws which govern the use and disclosure of personal Health Information by NYSPI. This means that once your Health

Information has been disclosed to a third party which does not have to follow these laws (e.g., a drug company or the Sponsor of the Research), it may no longer be protected under the HIPAA or NYS Mental Hygiene Law requirements but is subject to the terms of the consent form and may be subject to other state or federal privacy laws or regulations.

4. Please note that:

- You do not have to sign this Authorization form, but if you do not, you may not be able to participate in the study or receive study related care. You may change your mind at any time and for any reason. If you do so, you may no longer be allowed to participate in the study. If you withdraw this Authorization the research staff and the Sponsor, if this is sponsored research, may still use or disclose Health Information containing identifying information they already have collected about you as needed to maintain the reliability of the research. Any request to withdraw this Authorization must be made in writing to (enter name and contact information below):

Daniel Javitt, M.D, Ph.D, 1051 Riverside Dr-Unit 42, New York, NY 10032

- While the Research is going on, you may not be allowed to review the Health Information in your clinical research record that has been created or collected by NYSPI. When this research has been completed you may be allowed to see this information. If it is needed for your care, your Health Information will be given to you or your Doctor.

5. This Authorization does not have an end date.

6. You will be given a copy of this form after you have signed it.

I agree to the use and disclosure of Health Information about me as described above:

Signature of Participant/ Legal Representative

Date

Printed Name of Participant

Relationship of Legal Representative to Participant (if applicable)

We also ask you or your legal representative to initial the statements below:

I have received a copy of the NYSPI/OMH Notice of Privacy Practices.