Official title: **Remediation of auditory recognition in schizophrenia with transcranial direct current stimulation (tDCS)**

NCT number: NCT02869334

Document date: 10/27/2016

NATHAN KLINE INSTITUTE/ROCKLAND PSYCHIATRIC CENTER
INSTITUTIONAL REVIEW BOARD

IRB Office Telephone: (845) 398-5493 or 398-5492

APPLICATION FOR APPROVAL OF NEW PROTOCOL

DATE: 8/29/2016
Modifications required: 10/27/2016

PROTOCOL TITLE: Remediation of auditory recognition in schizophrenia with transcranial direct current stimulation (tDCS)

DOCUMENTS SUBMITTED WITH THIS APPLICATION (Include a list of all documents submitted, including protocol, consent forms, advertisements, etc., with version date for each. Include all information required for the IRB approval letter):
Cover memo 9/28/2016/
Cover memo(response to conditions/modifications required dated 10/24/2016
Application for Approval of New Protocol 8/29/2016/modifications required version 10/24/2016
Protocol 8/29/2016/modifications required version 10/27/2016
Examples of Session flow charts with list of study procedures(for Auditory remediation/tDCS computer training conditions and for game computer training condition)
Consent form 8/29/2016/modifications required version 10/27/2016
Scope of Work-requested by IRB for response to conditions submission
Progress report-included in response to conditions submission
HIPAA addendum 8/29/2016
Waiver of consent 8/29/2016
Phone Screening Script 9/28/2016
NKI Notice of Privacy Practice
Copies of CITI training and CVs for Odeta Beggel, Constance Shope, Anastasia Stoops
Uploaded training and credentials for Drs. Javitt, Dias, Kantrowitz, Sehatpour and for Gail Silipo

PRINCIPAL INVESTIGATOR'S NAME, TITLE & TELEPHONE NUMBER:

The NKI site principal investigator is Elisa Dias, Ph.D. 845-398-6541
The overall principal investigator is Daniel Javitt, M.D., Ph.D. 845-398-6534

Name and telephone number of contact person, if different:
For details regarding the study for the IRB initial review please contact: Daniel Javitt, M.D., Ph.D. 845-398-6534 or Joshua Kantrowitz, M.D. at 845-398-5503
For other IRB issues contact Gail Silipo 845-398-6536

Co-Investigators (or Sponsor for research fellow or student):
Odeta Beggel, M.A.
Constance Shope, Ph.D.
Anastasia Stoops, Ph.D.
Gail Silipo, M.A.
Joshua Kantrowitz, M.D. is the study clinician and the safety monitor
Pejman Sehatpour, Ph.D.
STUDY/RECRUITMENT SITES: List all sites involved in subject recruitment and/or conduct of the study. (If subjects will be recruited from the community, state from what community - Rockland County,

Westchester County, etc.)
Recruitment sites for patients will include inpatients from Rockland Psychiatric Center who have been transferred to the inpatient research unit at NKI (Clinical Research and Evaluation Facility (CREF). We will also recruit outpatients through the Volunteer Recruitment Program (VRP) at NKI. The Volunteer Recruitment Program at NKI recruits from NYS office of Mental Health facilities. The VRP also recruits outpatients living on the grounds at CLUE I and II, Conway House(Loeb House), from Rockland County Department of Mental Health facilities and from the community. We will also invite patients who have participated in IRB approved studies conducted by Daniel Javitt, M.D., Ph.D., to participate in this protocol (those who have agreed to be recontacted for other studies).

FUNDING INFORMATION:
_____ No external funding
_____State
___√___ Federal Grant # __*R33MH099265*_____
_____ Other (Name of agency/company/private sponsor)_____

Please indicate which institution grant is funded through:
RFMH _√_____; NYU _____; Other _____ specify: __*Funded to NYSPI/Columbia and NKI is a subcontract (subcontract to NKI in process).*

Is this a multicenter trial? Yes _____ No__√____ If yes, indicate # of sites _____

IS THIS A CLINICAL TRIAL? __√___YES ___NO

CLINICAL TRIAL REGISTRATION: Controlled clinical investigations, other than Phase 1 studies, of a product subject to FDA regulation must be registered on clinicaltrials.gov. (This includes IND-exempt clinical trials). Please provide NCT #__ *NCT02869334*_____ Identity of Responsible Party Daniel Javitt, M.D., Ph.D. is the overall study PI.
Dr. Javitt/Dr. Kantrowitz will update the information in clinical trials.gov
Does this research require an IND or IDE? Yes _*has an abbreviated IDE*___ No ____ ; If yes, provide the number *CE Reg#MED30003* and name the person/entity that holds the IND or IDE *Brainvision LLC.*
Note: The study may not begin until this information is provided to the IRB office.

PLEASE ANSWER IN LAY LANGUAGE WITHOUT JARGON, TECHNICAL TERMS OR UNDEFINED ABBREVIATIONS. ALSO, ATTACH FULL PROTOCOL WHICH CONTAINS A BACKGROUND SECTION, THE AIMS AND OBJECTIVES OF THE PROJECT, A FULL DESCRIPTION OF THE EXPERIMENTAL DESIGN AND PROCEDURES, AND AN EXPLANATION OF HOW DATA WILL BE ANALYZED AND INTERPRETED.

A. IRB Submission Abstract

All IRB submissions must be accompanied by a submission abstract. The abstract, at a minimum, should include the elements as per below. Be complete yet concise; restrict your abstract to 2 pages, and expand on the components in the abstract in the other sections of this application as required.

Outline of the IRB Submission Abstract
1. Brief Introduction (2-3 sentences)
2. Specific Aims/Hypotheses (list and explain in bulleted format)

3. Research Participants
    a. Number
    b. Method for Ascertainment
    c. Inclusion/Exclusion Criteria
    d. Relevant safety cut point (s) for dropping subject from the study
4. Research Procedures
5. Risks
6. Consent Process
7. State whether any drugs tested are approved by FDA, are under an IND (Investigational New Drug Application), or are marketed products being used "off-label".
8. State whether any devices are under an IDE or Abbreviated IDE
9. Issues requiring special attention of the IRB

1. Abstract of Protocol:

Schizophrenia is associated with impairments in basic auditory functions, such as the ability to match tones following brief delay. These impairments contribute to difficulties that patients have in detecting emotion based on tone of voice (auditory emotion recognition, AER) along with other auditory functions such as sounding out words during reading (phonological processing). Schizophrenia patients also have difficulty in benefiting from remediation exercises designed to correct these deficits.

Transcranial direct current stimulation (tDCS) is a form of non-invasive brain stimulation in which low level electrical currents are applied to the scalp in order to manipulate brain function. In the present study, tDCS will be paired with auditory training to remediate deficits in basic auditory function in schizophrenia with the goal of assessing the tolerability and feasibility of this approach.

Patients will receive 34 sessions of auditory remediation over approximately 12-17 weeks. A total of up to 60 individuals will be enrolled and of the 60, it is anticipated that 45 individuals with a diagnosis of DSM-IV Schizophrenia or Schizoaffective Disorder who have auditory sensory deficits (as reflected in a score of <65% correct on the tone matching task) will complete the study. Patients will be randomly assigned to one of 3 groups: 1) auditory remediation with active tDCS; 2) auditory remediation with sham tDCS; 3) computer video-game remediation.

Behavioral measures (e.g. auditory emotion recognition) and EEG/event-related potential (ERP) measures (e.g. mismatch negativity; MMN) will be used to evaluate effects of the tDCS and training methods.

2. Specific Aims and Hypotheses

The Specific Aims are:

- *To evaluate effects of transcranial Direct Current Stimulation (tDCS)-enhanced auditory remediation on specific measures of auditory function. Patients will receive 34 sessions of auditory remediation over approximately 3-4 months. 45 individuals with a SCID diagnosis of DSM-IV Sz or Schizoaffective Disorder who have auditory sensory deficits (<65% on tone matching task) will be enrolled (complete the study). Patients will be randomized to 1 of 3 program trainings: 1) auditory remediation plus active tDCS; 2) auditory remediation plus sham-inactive tDCS; 3) computer video game remediation.*

- *To assess changes in auditory function after auditory remediation. This will be assessed using event related potentials (ERP) and electroencephalographic (EEG) measures pre/post completion of the tDCS program training. The ERPs and EEG measures will include auditory event related potential component N1 and P3, mismatch negativity-MMN, auditory steady state response- ASSR.*
- *To evaluate effects of tDCS-enhanced auditory remediation on neurocognition, functioning, social skills, reading and symptoms. These will be obtained before and after completion of the program training.*
    1. *Neurocognition measures will include: MATRICS Consensus Cognitive Battery (MCCB) and Processing Speed Index (PSI).*
    2. *Social Cognition measures will include: Auditory Emotion Recognition (AER), Penn Emotion Recognition Test-40 Faces Version (ER-40), and the Awareness of Social Inference Test (TASIT).*
    3. *Functioning measures will include: The University of California Performance-based Skills Assessment (UPSA), Global assessment of function (GAF) and the Specific Levels of Functioning Assessment (SLOF).*
    4. *Social skills measure will include: The Social Skills Performance Assessment (SSPA).*
    5. *Reading measure will include the Comprehensive Test of Phonological Processing-2 (CTOPP).*
    6. *Symptoms measure will include: Positive and Negative Syndrome Scale (PANSS).*

- *To evaluate potential mediators of response of both tDCS and cognitive remediation efficacy using plasma D-serine and BDNF levels. These will be obtained at study baseline and after completion of the tDCS program training.*

- *To assess target engagement. It will be measured using the Intrinsic Motivation Inventory for Schizophrenia (IMI), Perceived Competency Scale (PCS) and Treatment Motivation Questionnaire (TMQ) scales.*

The Hypotheses are:

- *There will be objective evidence of improvement in brain function as reflected by auditory ERP generation*

- *There will be moderate or greater effect size improvement of active tDCS/auditory remediation vs sham tDCS/auditory remediation.*

- *There will be a large or greater effect size improvement of tDCS/auditory training vs. (control) game training on specific cognitive measures(e.g. tone matching, AER, verbal learning, reading).*

3. Research Participants

a. Number

We project we will need to enroll 60 subjects to obtain the 45 completers which is the required number to accomplish study aims.

b. Method for Ascertainment

Potential candidates (patients) will be identified based upon their present diagnosis of schizophrenia or schizoaffective disorder based upon referral from their primary clinician, chart reviews or the volunteer recruitment pool.

c. Inclusion/Exclusion Criteria

All attempts will be made to maintain patients on stable doses of antipsychotic throughout the study. Subjects will be permitted to have dose changes for side effects. In cases of worsening of symptoms, increases of up to 50% of dose will be permitted without removing patients from the study.

The following adjunctive medications are allowed: beta-blockers; mood stabilizers, antidepressants; and anti-anxiety agents. PRN doses of clinically determined benzodiazepines or antipsychotics will be permitted. Given a possible detrimental effect on cognition, regular use of benzodiazepines will be considered covariates in the analysis, and patients will be asked to not take these medications for 3 hrs prior to testing/training session if clinically feasible. Participants receiving adjunctive anticholinergic medication will be excluded.

Inclusion Criteria	*Method to ascertain*
Age 18-55	*Clinical evaluation and/or medical history; self report*
Primary diagnosis of Schizophrenia or schizoaffective disorder	*Clinical evaluation and/or medical history*
SCID primary diagnosis of DSM-IV schizophrenia or schizoaffective disorder	*SCID*
English fluency	*Interview*
Willing/capable to provide informed consent Capacity to Consent	*Capacity assessment by licensed professional*
IQ≥75	*WRAT, Clinical evaluation, medical history*
Score <65% on tone matching	*Tone Matching Test*
Normal Hearing	*Audiometry testing, examination corresponding to a reduction of 1.5 sd vs. HV*
Receiving stable antipsychotic medication for >2 weeks	*medical history, medication records, clinical evaluation* (criteria used in prior studies)

Exclusion Criteria	*Method to ascertain*
Serious neurological disorder or medical condition/ treatment known to affect the brain. Neurological Disorder that affects the central nervous system (CNS), such as epilepsy, neurodegenerative disorders, movement disorders and sensory disorders.	*Clinical evaluation, medical history*
Active suicidal ideation	*Affirmative answers to items 3, 4 or 5 of the Suicidal ideation section of the screening and pre testing Columbia Suicide Severity Rating Scale (CSSRS) in the 6 months prior to screening or subject who represent a significant risk of suicide in the*
Current or past history (within last 6 months) of substance abuse or dependence (excluding Nicotine)	*Clinical evaluation , medical history, urine toxicology, SCID*
Pregnancy or breastfeeding	*Urine Pregnancy Test, self report, medical records*
Taking Adjunctive anticholinergic medication (i.e. Cogentin, Benztropine)	*Clinical evaluation, medical history, medication records, self report*
Participation in study of investigational medication within the past 4 weeks (prior to screening) or investigational device within the past 4 weeks (prior to start of tDCS training)	*Self report*

d. Relevant safety cut point (s) for dropping subject from the study

Subjects will be withdrawn from the protocol by the study clinician, if any of the following should occur:

-The subject experiences a clinically significant adverse event, which, in the clinical judgment of the investigators/study clinician, would increase the risk to the welfare of the subject and be inconsistent with continuation in the study.

-Clinical worsening: Clinical worsening will be defined as a > 20% increase in PANSS total symptom score from baseline. In the event this occurs, the study clinician will speak with the

patient, and his/her treating psychiatrist will be notified. The participant will be referred to their primary psychiatrist for re-evaluation, who will then determine if the patient requires changes to his/her medication regimen and if he/she should continue in the protocol or be exited for safety reasons. Patients who are judged by the study clinician to require emergency intervention due to clinical deterioration will be referred to the local hospital emergency department for further evaluation.
-Pregnancy: If any urine test is positive for pregnancy or the subject reports becoming pregnant, the participant cannot to continue with tDCS training sessions and she will be withdrawn from the study.

-Withdrawal of participant consent

-Subject noncompliance, defined as refusal or inability to adhere to the study schedule or procedures. Missing sessions will be reviewed as to the reasons why and if it is found that the individual is failing to adhere to study requirements a decision will be made as to whether the individual will remain in the study. This will be done on a case-by-case basis.

4. Research Procedures
The present study evaluates tolerability and feasibility of repeated administration of tDCS and auditory remediation alone and in combination.

All participants will receive an eligibility screening, which includes demographics, psychiatric and medical history, SCID, assessment of auditory function and auditory emotion recognition, urine toxicology and, if applicable, pregnancy tests, and related measures (~2 hours).

After consenting and establishing eligibility, each participant will be asked to participate 3 behavioral sessions (behavioral sessions can be combine into one or 2 sessions if preferred, each session is ~2 hours or ~ 6 hours total), one ERP/EEG session (~ 3 hours) and a blood draw (~ 5 minutes). These assessments will be repeated at the end of the study, following completion of all training sessions.

Once the assessment sessions are completed, each participant will be assigned randomly to 1 of 3 study arms: 1) active auditory remediation/training + active tDCS; 2) active auditory remediation/training + sham tDCS; 3) computer game condition ("control" remediation). Each training type involves two or three sessions per week, approximately 30 minutes each, for approximately 12-17 weeks (34/30 minute tDCS training sessions) depending on the number of sessions per week the subject is able to attend

1. Eligibility Screening:

After the patient signs the informed consent form and the HIPAA authorization, he/she will undergo a diagnostic interview (SCID) and brief audiometric examination to insure adequate hearing ability, and will complete a simple behavioral test of auditory processing to determine the presence/absence of auditory sensory deficits (Tone Matching Test), and brief evaluation (WRAT Reading) to estimate premorbid intellectual ability. Also a screening for active suicidal ideation (Columbia Suicide Severity Rating Scale) will be completed

Females of childbearing capacity will receive a urine pregnancy test; tDCS cannot begin unless a negative result is obtained.

A brief clinical evaluation and/or medical history will determine medication history and presence/absence of current alcohol or drug abuse. Additionally, a urine toxicology test will be performed to verify substance use. The total eligibility session length will be approximately 2 hours.

2. Pre-training assessments

2.1 Behavioral Assessment

The total behavioral assessment length will be approximately 3 sessions (can be combined into 1 or 2 sessions), 2 hour each session (6 hours total).

Behavioral assessments include standardized measures of neurocognition (MATRICS Consensus Cognitive Battery, Processing Speed Index of the WAIS-4), social cognition (Auditory Emotion Recognition, Penn Emotion Recognition Task, The Awareness of Social Inference Test), functional (i.e. everyday life) skills (UCSD Performance-based Skills Assessment, Global Assessment of Function, Specific Levels of Functioning Assessment), social skills (Social Skills Performance Assessment), and reading ability (Comprehensive Test of Phonological Processing). Assessment of current psychiatric symptoms will include the Positive and Negative Symptom Scale and the Columbia Suicide Severity Rating Scale, The Assessment for Treatment Emergent Events (SAFTEE) to assess current preexisting health issues prior to the start of the tDCS training sessions.

2.2 Electroencephalography/Event Related Potential (EEG/ERP) sessions

An EEG session will be completed before the experimental procedures. Electroencephalography (EEG) will be used to continuously record electrical brain activity from the scalp while subjects complete the tasks described below. In addition, 10 minutes of resting eyes open/closed EEG will be obtained, leading to 1:45 hr total recording time. The total session length, including the application and removal of the electrode cap and any required breaks, will be approximately 3 hours. Based upon our prior experience, we expect this session length to be tolerable even for cognitively impaired individuals.

EEG data will be obtained from Brain Vision electrode system with 24- 64 scalp electrodes, digitized at 500-1000 Hz. digital recording system (Brain Product GmbH, Gilching, Germany).

ERP will be obtained to synthetic FM-tones that differ in pitch, intensity or HF500. The FM-tones were developed by measurement of acoustic cues of the Juslin and Laukka's prosody stimulus set. FM-tones were synthesized (Adobe Audition) to be 500 msec in length with a modulation frequency of 3 Hz (1½ cycles per tone), at a nominal intensity of 75 dB sound pressure level (1). The "standard" tone had moderate levels of F0M and F0SD (e.g., an F0M/F0SD of 125/125 Hz), and was designed to be emotionally ambiguous, while the deviants were designed to mimic specific emotions. The six deviants were modified from the standard tone as follows:

1) F0M: increased base pitch with unchanged pitch variability (i.e. 378 Hz/125 Hz); typically perceived as happy.

2) F0SD: unchanged base pitch with decreased pitch variability (i.e. 125 Hz/20 Hz); typically perceived as sad.

3) HF500: adding an overlay of HF500 noise with unchanged pitch characteristics; typically perceived as angry or fearful.

4) Intensity: increasing the intensity (volume) to 85 dB with unchanged pitch characteristics; typically perceived as angry or fearful.
5) Dual (F0M/F0SD): varying both base pitch and variability (378 Hz/20 Hz); leads to a stimulus that differs physically from the standard, but does not convey a predominant emotion percept
6) Non-FM: a simple, non-FM modulated tone (125 Hz), which is perceived primarily as neutral or no emotion.
7) Stimuli will be presented through headphones with an interstimulus interval (ISI) of 250 msec. During MMN testing, subjects will not be informed of the emotional intent, and watch a silent, unrelated movie.

A multidimensional, "optimized" design will be used, allowing for multiple deviants to be assessed simultaneously. Four 950 tone blocks will be used, with each block divided into an "oddball" section, followed immediately by a "repetitive N1" section. In the oddball section, 600 tones will be presented: Standard tones (300 total/50%) alternated with one of the six deviants (50 of each deviant tone per block ~8.33% for each deviant). The deviant tone cannot be the same as one of the previous four deviants. In the repetitive N1 section, 50 repeats of each of the seven tones (350 total tones, 50 each) will be presented. Thus, each tone was presented both as a deviant against a background of the more frequent, emotionally ambiguous "standard" stimuli in the oddball section and repetitively in the "repetitive N1" section.

All standardized assessments (behavioral and electrophysiological) and interviews will be conducted by a trained rater. Dr. Elisa Dias will supervise collection of assessments and electrophysiology.

2.3 Blood Draw

BDNF/D-serine levels will be obtained at study baseline and after completion, and will be evaluated as potential mediators of both tDCS and cognitive remediation efficacy. Any additional blood remaining will be kept frozen at -70°C to be used if other potential biomarkers are developed over the course of the study.

3. Computer-based Training sessions

After the first and final experimental training sessions, participants will complete questionnaire-based measures of motivation (Intrinsic Motivation Inventory, Perceived Competency Scale, Treatment Motivation Questionnaire) to assess engagement.

Eligible participants will be randomly assigned to one of three training programs:
1) auditory remediation plus active tDCS;
2) auditory remediation plus sham tDCS;
3) computer game.

All programs are 2-3 sessions per week of at least 30 minutes each tDCS training session, conducted over approximately 12-17 week period (34 tDCS training sessions total). During the auditory remediation training sessions subjects will receive either active or inactive tDCS. During the computer game program subjects will not receive active or sham tDCS.

Participants in the auditory remediation conditions will sit at individual computer workstations and respond to auditory stimuli presented through headphones. Auditory exercises will entail computer-based activities designed to train ability to identify and differentiate between tones that vary in pitch, intensity, and frequency. The exercises provide feedback to participants to facilitate learning of acoustic cues to improve accuracy of auditory stimulus identification and discrimination. Level of difficulty for stimulus identification or discrimination is programmed to vary based on the performance of each individual such that as performance improves, task difficulty increases. After each tDCS training session, discomfort with tDCS will be assessed using the Wong-Baker Faces Pain Rating Scale and the Brunoni Questionaire for tDCS. At the conclusion of each weekly session, participants will engage in a 10-minute discussion with the facilitator to bridge computer-based training to everyday life. No tDCS will be given during weekly discussion. Discussion for active training will include topics aimed to enhance motivation for the exercises by providing a personally relevant functional context for auditory training. Discussion will also include study progress, enjoyment of computer activities and any issues relating to session adherence. Also at the conclusion of every other weekly session (biweekly) and at the conclusion of the last week of training, clinical and medical symptoms will be assessed.

The computer game is the condition where participants will work on commercially available puzzle games to control for clinician contact and the non-specific effects of mental stimulation. The schedule of computer-based activity will be the same as the auditory remediation. Participants will engage in a once weekly discussion with the session facilitator to discuss study progress, enjoyment of computer activities, and any issues related to session adherence. Also at the conclusion of every other weekly session (biweekly) and at the conclusion of the last week of training, clinical and medical symptoms will be assessed.

tDCS:

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). tDCS electrode placement will be over frontal areas and bilateral mastoids. Localization of electrode placement will be established using the 10-20 EEG technique. Each stimulation session will last~30 minutes.

tDCS stimulations will be administered by trained research staff member.
Females of childbearing capacity will receive a urine pregnancy test monthly during computer based training sessions. tDCS cannot continue unless a negative result is obtained.

4. Post-training testing

After completion of the computer–based training sessions, participants will be scheduled to complete post-training assessments which include behavioral tests, one session of EEG, and a blood draw as described above for the pre-training testing. They will also repeat the Tone Matching Task and the Audiometry (hearing test) that was done at screening.

5. Risks

<u>Transcranial Direct Current Stimulation (tDCS) procedures:</u> Risks associated with the tDCS procedures for this study are similar to risks associated with other tDCS studies, which are

minimal. tDCS is presently a widely used research technique, most commonly in the areas of motor rehabilitation and depression.

The risks to human subjects directly associated with tDCS administration include:
a) Mild tingling sensation at the site of application during administration.
This sensation ceases after treatment is completed.
b) Mild headache
c) Slight epidermal irritation, redness or burns at site of application
d) Mild temperature changes at the site of application.

The dosing of tDCS proposed in this study (2 mA x 20-40 min) are within the range used in recent and ongoing clinical studies. For example, in a recent study of 131 healthy subjects undergoing 277 tDCS sessions, no serious adverse events occurred. Side effects most commonly reported were tingling (76%), itching (68%), burning (54%), and pain (25%). Side effect severity was mild, with fewer than 2% of responses indicating a severity > 3 on all questions except tingling (15%), itching (20%), burning (7%), pain (5%), and fatigue (3%) during stimulation. Symptoms resolved promptly following termination of stimulation without long-term consequences. In rare cases, nausea or insomnia have been reported. Although formal toxicity studies have not been performed, doses of tDCS used in present clinical studies are at least two orders of magnitude below those that have been shown to produce brain lesions in rodent.

Worsening of psychiatric condition: In addition to common tDCS side effects, the risk of repeated tDCS exposure in Sz is presently unknown. We have performed >100 individual sessions in patients with Sz without observing adverse effects on symptoms. Furthermore, in disorders such as depression, therapeutic effects have been observed from bifrontal tDCS. Nevertheless, given the lack of information there is a possibility of worsening of either symptoms or cognitive function (PANSS). These potentials will therefore be monitored biweekly by an independent safety monitor, as detailed in section procedures for minimizing risks below. As with all trials, there is a risk for development of suicidal ideation, which will be monitored biweekly using the Columbia-Suicide Severity Rating Scale as well.

Electrophysiological EEG procedures: These studies entail the recording of EEG from the scalp employing standard sensors and amplification methods. These procedures are well standardized and there are few known risks. These are principally due to equipment malfunction.
The recording equipment used in these studies meet the current design criteria for subject safety, including isolation from potential electrical hazards.

Assessment/screening procedures: There are no known physical or psychological risks involved in taking these tests. Subjects may find the interviews about their psychiatric condition upsetting, and although the test procedures are designed to be relatively simple, some subjects might experience some frustration during the tests.

Confidentiality: There is a risk from study participation of loss of confidentiality

Describe procedures for minimizing risks

tDCS: Mild headache has been reported when tDCS is administered in some cases, but has been known to cease with acetaminophen, ibuprofen, or aspirin. Slight epidermal irritation at sight of application has been reported in some instances. Mild temperature change might be felt at the site of application.

During the period of administration, the participant will be closely and regularly observed and asked to report any adverse effects. Subjects may opt to discontinue at any point. We will also regularly debrief subjects following tDCS sessions to detect patterns or procedures that might be associated with discomfort and will modify procedures as necessary.

Additionally, we will monitor discomfort using Wong-Baker Faces Pain Rating Scale (WBFPRS) which we feel is readily understood by patients and provides general evaluation of discomfort. To date, data have been collected from 37 patient sessions in which active stimulation was used and 15 sham session. Discomfort during the active stimulation session was generally low (mean WBFPRSscore = 0.51 ± .87), corresponding to between "no-hurt" and "hurts little bit". During sham, the mean scores were also low but non-zero for many subjects (mean score=.33 ± .82). The difference between scores was not significant (p=.48). No patient scored above a 2 on the scale, and no patient discontinued due to discomfort.

In addition, we will incorporate additional measures as suggested by Brunoni et al. (24) to monitor discomfort and potential objective adverse effects of tDCS (e.g. skin redness).

During this study, blinded Adverse Effects Summaries (AES) will be provided to the independent monitor who will evaluate to insure that adequacy of protection against risk is maintained, and will provide feedback to the PI and the research teams. In addition, any scores of 4 or 5 on the WBFPRS will be brought to the immediate attention to the PI, who will then review clinical procedures.

Headache and dizziness are also known risks of tDCS. Anyone experiencing such symptoms will be monitored until symptoms resolve, and will be recontacted 24-48 hrs after the event to insure that there were no long-term sequelae.

Adverse Effects (AEs) and Serious Adverse Effects (SAEs) will be reported to the IRB as per standard protocol, and will lead to review of procedures to determine whether alterations in the protocol or monitoring procedures are required.

<u>Worsening of psychiatric condition:</u>
In order to detect potential worsening of symptoms, patients will be assessed with the Positive and Negative Syndrome Scale (PANSS) ratings biweekly during the training program. PANSS ratings, including positive, negative and cognitive factors, will be reviewed in a non-blinded fashion by the independent monitor to insure that there is no significant worsening in the tDCS vs. sham group.

In addition, subjects showing >10 pt worsening on PANSS or > 2 pt worsening on psychosis items will have case reviewed to determine potential causes and, if appropriate, will have tDCS/AR treatments temporarily withheld for up to 2 weeks. All attempts will be made to maintain patients on stable doses of antipsychotic throughout the study. However, in cases of worsening of symptoms, increases of up to 50% of dose will be permitted without removing patients from the study.

In addition to PANSS ratings, we will also maintain close contact with treating clinicians and instruct them to contact the research team should they notice worsening of symptoms during clinical treatment.

Suicidality: It is expected that patients participating in this study will be clinically stable. Nevertheless, because tDCS may affect mood symptoms and because effects of repeated tDCS in Sz are unknown, patients will be rated biweekly using the Columbia-Suicide Severity Rating Scale (25,26). Significant suicidal ideation will be reported immediately to the PI or his designee, who will insure appropriate treatment intervention.

General side effects: General side effects will be assessed biweekly using the Systematic Assessment for Treatment Emergent Events (SAFTEE) scale (27), and will be provided in a unblinded fashion to the independent monitor. All significant side effects will be reported to the PI, and appropriate intervention will be initiated.

Independent individual/safety officer: Because of potential discomfort induced by tDCS, Dr. Joshua Kantrowitz will serve as an unblinded independent individual/safety officer. Dr. Kantrowitz is a board certified psychiatrist. Dr. Kantrowitz will have access to unblinded subject safety ratings biweekly, and will monitor quarterly the side effect frequency between groups. Dr. Kantrowitz will notify the PI should there be significant imbalance in rate of side effects between active and sham treatment, in which case appropriate adjustments will be made to the sham stimulation protocol, or if an excess of painful events occur (Wong-Baker score >3), in which case procedures which be reviewed. Dr. Kantrowitz will also review biweekly subject PANSS, suicide (CSSRS scores), and SAFTEE scores to insure that no unanticipated side effects are observed.

Electrophysiological EEG procedures
Regular preventative maintenance and careful attention to recording procedures further minimize the already insignificant risks of electrophysiological recording. Electrodes and materials used for affixing them in place are kept scrupulously clean and sterilized and materials are utilized which minimize the chance of skin and scalp irritation

Patients will be instructed to clean their hair following the procedure to minimize irritation.

Subjects may find it upsetting to discuss their medical or psychiatric problems, but this is not different from interviews conducted during routine medical care. Participants may find the EEG or computer tasks tiring or difficult and may experience mental fatigue and transient stress from the neuropsychological testing.

Blood drawings: Phlebotomy will be performed by trained phlebotomist using sterile technique to minimize possibility of contusion or infection.

Assessment/screening procedures: Frequent breaks will be given as needed. Subjects will be reassured that they will not have to answer questions that cause discomfort.

Confidentiality: Every effort will be made to protect the participant's confidentiality.

6. Consent Process

Subjects selected for the study will be fully informed of the nature and scope of the study. Research study staff who have had consent training through the Clinical research division will meet with interested prospective participants. A complete description of the protocol will be given including potential risks and benefits and other significant elements of the consent (including confidentiality, voluntary nature of research). In addition, prior to approaching patients, we discuss patients who meet eligibility criteria with their treatment teams. For CREF

inpatients, we will be in contact with the patient's treating psychiatrist, and for outpatients, we will be in contact with a member of the patient's treatment team/patient's doctor to discuss the study and the patient's participation. The consent process involves review of the consent form and the HIPAA addendum, along with additional elaboration of all elements and answering any questions the participant may have and asking questions to assess the participant's understanding of the informed consent document. When all of the participant's questions have been answered and the research study staff is satisfied that the participant understands the study, has had an opportunity to evaluate the risks and benefits of participation and voluntarily consents to participate in the study, the participant and the research study staff member will sign the informed consent document.

Consent to participate by CREF inpatients and RPC outpatients is documented in their electronic medical record in the form of a chart note and consent form. Records of informed consent for all participants are maintained in the subject's research record. The subject is given a copy of their consent form and a copy of the NKI Privacy Practices form.

Capacity will be assessed by the Treating Psychiatrist or licensed professional who is not directly involved in the research.

7. State whether any drugs tested are approved by FDA, are under an IND (Investigational New Drug Application), or are marketed products being used "off-label".
   No drugs are tested for this study.

8. State whether any devices are under an IDE or Abbreviated IDE

   The device, BrainStim SYS (Brainvision LLC,Germany), has an abbreviated IDE
   CE Reg#MED30003
   There is a label on the device which contains: the name of the device, the manufacturer, a model and serial number. We have placed a label on the device that states: "CAUTION-- Investigational device limited by Federal (or United States) law to investigational use." Since the device itself is quite small, an additional label with all warnings and precautions will not fit on the device. We have placed a label on the device case.
   The manual for the device is located in the device case (where we keep the device when not in use) and it describes all relevant warnings and precautions. We have a label on the device case that states: "This case contains the device manual describing all relevant warnings and precautions".

9. Issues requiring special attention of the IRB
   None.

B. SUBJECT POPULATION:

Sample Size:
We project we will need to enroll 60 patients in order to have 45 completers.

Age Range (indicate whether children, subjects under age 18, will be enrolled):
18-55

Diagnostic Groups:
Schizophrenia or Schizoaffective Disorder

Ethnic, Race and Gender Breakdown:
Participants will be representative of the respective population (ethnicity, race and gender) at the recruitment site. No racial or ethnic group will be specifically included or excluded.

Also, indicate below whether the sample represents the minority and gender distribution of the population or immediate geographic area from which the sample is drawn. Explain if any specific groups are excluded. Indicate whether each gender and minority group will be represented in sufficient numbers to allow statistical analysis of the results for each group. Explain if the representation will not be sufficient. Note: Although every effort should be made to include sufficient numbers of women and minorities, there are acceptable reasons why this cannot or need not always occur such as pilot studies, condition limited to one gender, limited access, limited resources, or multi-center studies where total numbers will be representative. If gender and/or minorities are excluded, provide a clear rationale for their exclusion.

No racial or ethnic group will be specifically included or excluded. Participants will be representative of the respective population (ethnicity, race, and sex) at the recruitment site.

C. RECRUITMENT METHODS:

- If **advertising** for subjects, describe the process and attach to this form any letters to be sent, texts of advertisements or other material to be used in recruitment. If not available now, this material must be approved by the IRB before use.

We will not be advertising at this time. If we decide to advertise, we will submit material to the NKI IRB for approval first.

- If **screening** patient medical records to identify possible subjects, please so indicate below and complete the form **"Request for HIPAA Waiver of Authorization and/or Waiver of Consent under 45 CFR 46.116(d)"**.

  Screening will be done by staff in our division. A HIPAA Waiver of Consent is attached and a phone screening script.
  We will use the phone screen to call outpatients that have been referred to us by the Volunteer Recruitment Program (VRP) at NKI. The Volunteer Recruitment Program at NKI recruits from NYS office of Mental Health facilities. The VRP recruits outpatients living on the grounds at CLUE I and II, Conway House(Loeb House), from Rockland County Department of Mental Health facilities and from the community. We will use the phone screen to see if the outpatient is interested in participating in the study and to obtain any screening information specific to this study. We will also use the phone screen to call outpatients who have participated in IRB approved studies conducted by Daniel Javitt, M.D., Ph.D., (those who have agreed to be recontacted for other studies) to see if they are interested in participating in this protocol and if they are willing to answer phone screening questions. We do not have a treating relationship with these potential outpatients. If the outpatient meets phone screen criteria and agrees to come in and sign consent and the HIPAA addendum to participate in the study, prior to starting the intervention, we will to speak with the outpatient's psychiatrist about the study,

the outpatient's participation in the study(whether there is any issue with the subject participating in the study) and whether the psychiatrist's plans to keep the outpatient's medications stable.

We will also use the phone screen for outpatients who call from the community (i.e. saw study on Clinical trials.gov). If the outpatient is interested in participating in the study and in answering phone screening questions, we will obtain screening information. We do not have a treating relationship with these potential outpatients. If the outpatient meets phone screen criteria and agrees to come in and sign consent and the HIPAA addendum to participate in the study, prior to starting the intervention, we will need to speak with the outpatient's psychiatrist about the study, the outpatient's participation in the study(whether there is any issue with the subject participating in the study) and whether the psychiatrist plans to keep the outpatient's medications stable.

For CREF inpatients, we should be able to get the phone screen information from the medical records or the patient's treating psychiatrist on CREF. However, if we are unable to get screening information from medical records or patient's psychiatrist, we may need to speak to the patient on CREF and talk to them about the study and their willingness to answer some study specific screening questions. We will also speak to the treating psychiatrist about the patient's participation in this research (whether there is any issue with participating in the study and whether the psychiatrist plans to keep the patient's medications stable).

- If recruiting by **other means**, such as referrals from community physicians, please describe below.

We will not be actively recruiting from community physicians, however, we will accept referrals from the community (physicians, friends, and family of the patients).
We will use the phone screen for outpatients who call from the community (i.e. saw study on Clinical trials.gov). If the outpatient is interested in participating in the study and in answering phone screening questions, we will obtain screening information. We do not have a treating relationship with these potential outpatients. If the outpatient meets phone screen criteria and agrees to come in and sign consent and the HIPAA addendum to participate in the study, prior to starting the intervention, we will need to speak with the outpatient's psychiatrist about the study, the outpatient's participation in the study(whether there is any issue with the subject participating in the study) and whether the psychiatrist plans to keep the outpatient's medications stable.

D. RISKS AND BENEFITS:

1. Describe the risks presented by study procedures and interventions, including the expected frequency of the risks. Include all physical and nonphysical risks. (e.g., emotional distress, economic harm, legal jeopardy, breach of confidentiality).

Risks are described above in item 5. Risks

2. If the research presents more than minimal risk to subjects, describe all measures designed to minimize the risks. When applicable, describe inclusion, exclusion and drop-out criteria intended to minimize risks and describe any procedures for follow up such as when subjects are found to be in need of medical or psychological referral.

Minimizing risks are described above in item 5 . Risks

3. Describe any potential for direct benefit to individual subjects as well as the benefit to society based on the scientific knowledge to be gained. These two types of benefits should be clearly distinguished in your discussion.

E. CONSENT PROCESS AND PATIENT CAPACITY:

1. Indicate Who Will Obtain Consent, Assess Capacity, and Under What Circumstances: (Include name and title of these individuals)

Consent for this project will be obtained by Odeta Beggel, MA, Constance Shope, Ph.D. or Gail Silipo, M.A. All have had consent training through the Clinical Research Division. Capacity will be assessed by a Treating Psychiatrist or licensed professional who is not directly involved in the research. Capacity will be assessed by Drs. Fabien Tremeau, Russell Tobe or his designee in the Outpatient Research Division or Dr. Karen Nolan.

2. Will Individuals Potentially Lacking Capacity to Consent be Considered for Inclusion As Subjects:

No. Patients who lack capacity will not be considered for inclusion in this study. Capacity will be assessed by the Treating Psychiatrist or licensed professional who is not directly involved in the research.

If yes, list name(s) and title(s) of persons who will assess capacity (Note: The person(s) who assess capacity must be a psychiatrist or a licensed psychologist who is independent of the research.):

Capacity will be assessed by Dr. Fabien Tremeau, Dr. Russell Tobe or his designee in the Outpatient Research Division or Dr. Karen Nolan.

F. COMPENSATION:

Will subjects receive any compensation? Yes_√____ No_____
If yes, indicate how much and criteria for payment. Include method of pro-rating payment, if any, for subjects who do not complete the study.

Subjects will be paid $20 for the eligibility screening, $60 for the pre training behavioral assessments, and $30 ($10 per hour) for completion of the EEG research procedure and $5 for the blood draw. Subjects will be paid $10 per tDCS/training/discussion/and assessment sessions (34 sessions) for a total of $340 and $60 for the post behavioral assessments and $30 for completion of the post EEG and $5 blood draw. Subjects who complete the study will be paid a

bonus of $50. The maximum total amount for the whole study will be $600. Participants will be paid for the time completed. They will not receive the bonus if they do not complete the study.

G. CONFIDENTIALITY: Describe means by which privacy of both paper and electronic files will be protected and confidentiality maintained. If a Certificate of Confidentiality will be obtained, please indicate.

Note: All study data whether on paper or in encrypted electronic records or devices must be stored in locked files in a secured office. All electronic data containing PHI must be kept on the "HIPAA drive" or, when portability is required, on a hardware-encrypted device that has been approved by ISD.

Research information obtained will not be identified with participants' names; we will use a code. All paper data will be kept in locked cabinets and in locked offices. Electronic data will be stored in a HIPAA password protected directory. Any behavioral data that is collected on laptop computer will be collected on an ISD approved laptop that has been encrypted and has password protections which have been put into place by ISD.

H. CONFLICT OF INTEREST: In order for the IRB to determine whether financial interests pose a potential for bias that might affect the rights and welfare of the human subjects or the credibility of the research, please briefly describe any financial relationship the principal investigator or other researchers on this project may have with the study sponsor (other than funding this project) or any financial interest in the product being tested.

(**Note**: ""No conflict of interest" or "N/A" is not responsive to the question being asked. The question asks about financial relationships with the sponsor or financial interests in the product. These interests and relationships need not be conflicts. If no relationships or interests exist the answer should be "None" or a similar response.)

None.

I. OTHER ISSUES: Does this protocol raise any other sensitive issues concerning human subjects which would be of concern to the IRB or NKI Administration? If so, please elaborate.

No.