Psychosis Recovery and Research Center

Non-Invasive Direct Current Stimulation for Cognition in Schizophrenia

Clinical Protocol: Version 2.0 BCM
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Principal Investigator:	Raymond Cho, MD
Study Coordinator:	Megan Rafferty
Population:	Target sample Size: 40, male female, psychosis diagnosis Sub Study: Maximum of 20 participants
Number of Sites:	Single site Baylor College of Medicine is the enrollment site
Study Duration:	2 years
Subject Duration:	2 months Sub Study: 2 months

Objectives

Dorso-lateral Prefrontal Cortex (DLPFC) is critically involved the pathophysiology of cognitive disturbances in schizophrenia (SZ), a key determinant of functional outcome, yet poorly remediated by available medications (Green, 1996). Growing evidence supports DLPFC stimulation through transcranial direct-current (tDCS) - a noninvasive, nonconvulsive, well- tolerated and low-cost brain stimulation intervention – to be effective in improving some aspects of DLPFC function in SZ, while ameliorating refractory symptoms when targeted to the putative involved structure(reviewed in Mondino, 2015). However, the impact of DLPFC tDCS in SZ on critical cognitive dimensions, the associated neural mechanisms and functional outcome of the intervention has not been investigated. In this study, we aim to extend findings of tDCS effectiveness by pioneering its effect on such critical functions– namely, working memory (WM) and cognitive control (CC). Furthermore, we will pair behavioral assessments with neurophysiological investigations in order to provide mechanistic insights about tDCS effects: EEG, given the association of altered synchronized activity with symptoms on one side, with cortical excitability which is believed to be involved in tDCS effects [4,5]; MRI will provide the spatial resolution necessary to localize tDCS effects though fMRI and offer insights in their biochemical underpinning by spectroscopy methods. We will also assess the impact of tDCS on functional outcome and the mediating role of cognition and neurophysiological indices. Specifically, we propose a randomized double-blind parallel-arm study to assess:

Aim 1. The impact of tDCS on performance in CC and WM tasks. Hypothesis 1: Patients receiving active tDCS treatment will show an improvement in performance.

Aim 2. The relation of performance improvements to DLPFC neurophysiological and neurochemical indices. Hypothesis 2: Performance improvement by active tDCS is paralleled by: changes in key EEG synchronization indices (frontal gamma power and modulation of gamma power by theta phase), increased DLPFC BOLD activation and long term changes in spectroscopy fingerprints associated with glutamate and GABA.

Aim 3. The therapeutic effects on clinical symptoms and functional outcome. Hypothesis 3: Active tDCS will improve clinical symptoms (negative symptoms and auditory hallucinations) and functional outcome.

Sub Study:
Aim 1. The impact of tDCS on performance in CC and WM tasks. Hypothesis 1: Following active tDCS treatment, the participants will show an improvement in performance.

Aim 2. The relation of performance improvements to DLPFC neurophysiological indices. Hypothesis 2: Performance improvement, by active tDCS, is paralleled by changes in key EEG synchronization indices (frontal gamma power and modulation of gamma power by theta phase).

Aim 3. The therapeutic effects on clinical symptoms and functional outcome. Hypothesis 3: Active tDCS will improve clinical symptoms (negative symptoms and auditory hallucinations) and functional outcome.

Background Information
In the last 10 years, noninvasive, nonconvulsive brain stimulation has been actively researched as a treatment option for refractory symptoms. An intriguingly high effect size has been reported by tDCS (Brunelin, 2012), where the application of weak currents through the scalp, virtually imperceptible to the subject, has been shown to induce prolonged changes in cortical excitability. These are believed to arise from polarity-specific subthreshold membrane polarization shifts and modifications of NMDA receptor efficacy in the cortex underlying the stimulation site (Stagg, 2011). The most validated strategy, as exploited by Brunelin et al., targeted stimulation of the left temporo-parietal junction (TPJ) for hallucinations and the left dorsolateral prefrontal cortex (DLPFC) for negative symptoms. The observed improvements in negative symptoms are consistent with amelioration of baseline prefrontal excitability disturbances by anodal, excitatory stimulation. In spite of evidence supporting the central role of the DLPFC in the genesis of cognitive symptoms (Volk, 2006) and growing agreement on the dimensions critical in this interplay (c.f. NIMH Research Domain Criteria, http://www.nimh.nih.gov/research-funding/rdoc/index.shtml), no study to date has addressed the effects on such key prefrontal cognitive functions.

Prefrontal disturbances have been consistently reported in neurophysiologic studies of deficits in critical cognitive dimensions such as CC and WM. The demonstration of an association between frontal cortical γ disturbances and CC deficits (Cho, 2006) bridges behavioral findings with widely reported disturbances of synchronized high-frequency activity (Uhlhaas, 2012). Critically, such disturbances have been linked to post-mortem and molecular findings (Lewis at al, 2005) by models of excitation-inhibition imbalance, providing a rationale for tDCS based treatments.

Cognitive control – “a system that modulates the operation of other cognitive in the service of goal-directed behavior” [9] – is held as a core cognitive deficit in schizophrenia and is considered a construct that could be useful in dimensional investigations that span across psychiatric diagnoses. CC is critically recruited when prepotent modes of responding are not adequate. Accordingly, altered performance in SZ in the Preparing to Overcome Prepotency (POP) task, a cued stimulus-response reversal tasks, is associated with reduced engagement of prefrontal gamma activity. Updating and maintenance of goal-relevant information, such as object location in a spatial working memory (SWM) task, also induces frontal gamma activity. In these tasks gamma power is characteristically modulated by theta phase (theta-gamma coupling). While direct evidence of such coupling alterations in SZ has not been reported, convergent observations from both animal and human studies point to the functional relevance of the phenomenon and motivated the proposal of its involvement as the basis of WM dysfunctions in the disorder (Lisman, 2010). The employment of CC and WM tasks appears therefore to be particularly suited not only to track cognitive changes secondary to tDCS, but also to provide biomarkers that can inform translational models of the disorder and therapy.

Such neuronal synchronization changes can be robustly measured by EEG. MRI makes the challenge to localize their source in two ways: structural scans provide the anatomical information to advanced source localization algorithms and fMRI provide complementary information about DLPFC involvement in task execution. In the framework of the cellular machinery involved in the gamma cycle, excitation-inhibition balance shifts are tied

to the interplay between pyramidal neurons and fast-spiking, parvalbumin positive interneurons, which is neurochemically mediated by glutamate and GABA. MR spectroscopy correlates of tDCS – polarity specific effects on Glx:NAA and GABA:NAA (Stagg 2009) are consistent with involvement of this machinery and support the methodology to further detail DLPFC tDCS effects.

Study Design

This is an interventional study assessing efficacy and neurophysiological correlates of tDCS in schizophrenia patients in a randomized, double-blind parallel-arm design. The expected duration of the study is 2 years.

The following schematics outline the study design and the stimulation strategy. We will recruit 40 participants and may screen up to 60 people to achieve target subject population. Subject involvement will last approximately 2 months, including a stimulation session block - 2 daily 20 minute sessions over 5 consecutive days - and assessment sessions.

Participants will be pseudo-randomized into an active stimulation or sham stimulation arm, matched for cognitive impairment at baseline. Both acute and maintenance effects are evaluated through clinical and cognitive assessment and neuroimaging sessions at 4 time points baseline, after the first stimulation session, after 1 week and follow-up at 2 months.

Sub Study:

This is an interventional study assessing efficacy and neurophysiological correlates of tDCS in schizophrenia patients in a within subject design. The duration of the study will be in line with the 2 years of the main study. We will recruit a maximum of 20 participants. The participants will be recruited from the sham condition of the main study. After the two month follow-up (in the main study), the participants, who were randomized into the sham condition, will be asked to participate. Participation will be optional. Subject involvement will last an additional 2 months.

Study Population

We will recruit 40 subjects with a diagnosis of schizophrenia, schizophreniform disorder or schizoaffective disorder and taking antipsychotic medication. Medication history will be fully assessed with antipsychotic exposure converted into standardized equivalents.

Inclusion Criteria: a) ages 18-50 years; b) on stable doses of antipsychotic medication for at least one month; c) not taking benzodiazepines or mood stabilizers; d) Mild to severe cognitive impairment in MATRICS Consensus Cognitive Battery (composite scores < 40). Exclusion Criteria: a) DSM-5 mental retardation; b) significant head injury; c) medical illness affecting brain function or structure; d) pregnancy or postpartum (<6 weeks after delivery or miscarriage); e) significant neurologic disorder (e.g seizure disorder); f) inability to provide informed consent; g) significant color blindness that affects task performance; h) comorbidity for DSM-5 psychoactive substance use disorder within the past one month; i) positive urine drug screen (excluding THC at baseline); j) temporal relation between illness onset and head injury; and k) Taking benzodiazepines or mood stabilizers (lithium allowed).

Sub Study:

We will only recruit from the 20 participants who were randomized into the sham condition of the main study. Inclusion: Completion of the sham condition of the main study. Exclusion: Participation in the active stimulation condition of the main study. Additionally, if the participant has 1) become pregnant, 2) stopped their antipsychotic medication 3) began taking benzodiazepines or mood stabilizers (lithium allowed), or 4) met criteria for DSM-5 psychoactive substance use disorder within the past one month, they will no longer be eligible for the sub-study.

Subject recruitment

Subjects will be recruited from the outpatient clinical programs at Baylor College of Medicine and other community psychiatric programs. These will include Ben Taub's psychiatric emergency room and inpatient and outpatient center and MHMRA. Primary clinicians at BCM will be notified of our research study. Potential subjects with a diagnosis of schizophrenia will be identified and initially approached through their primary clinician, who will ask patient's permission to be contacted by the research team. Upon obtaining patient's written permission, a staff member from the research team will contact the subject. We will also recruit participants through flyers in the community and social media, such as facebook and BCM's clinical trials website.

<u>The screening and recruitment procedure is listed below:</u>

Screening:

-Eligibility checklist

-Ishihara Color Blindness Test

-Urine Pregnancy test for females

-Urine drug screen, if not available from inpatient/outpatient testing

Sub Study:

-Eligibility Checklist

-Urine pregnancy test for females

-Urine drug screen, if not available from recent inpatient/outpatient testing

<u>Screening before experimental procedures:</u>

-EEG and MRI screening protocol prior to participating in imaging studies

Symptoms and Neuropsychological assessment: Interviews and Ratings

Participants will be interviewed in a dedicated room at the Greenpark One building. One of the following two cognitive batteries may be administered. The BACS battery, a newly developed instrument that assesses cognitive impairments in schizophrenia takes approximately 35 minutes to complete. The constructs that are measured include verbal memory, working memory, motor speed, verbal fluency and executive functioning. The other cognitive assessment tool that could be used is the MATRICS assessment. The full MATRICS battery targets the six cognitive domains (speed of processing; attention/vigilance; working, visual and verbal memory; reasoning and social cognition) identified as being disturbed in schizophrenia. The MATRICS battery takes approximately 1 hour.

Sub Study:

MATRICS will be completed at the 1 week time point.

<u>Safety and tolerability assessment</u>

Clinical and neuropsychological assessments are all performed by trained research personnel to reduce the risk of distress from psychiatric interviews and experimental procedures.

Clinical Assessments

In addition to detailed demographic information (including medication and treatment information), we obtain diagnostic information using the Structured Clinical Interview for DSM-5 Disorders (SCID-5) and/or the MINI International Neuropsychiatric Interview for Psychotic Disorders Studies (MINI 7.0.2) at the discretion of the PI. Psychopathological ratings are conducted include: the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Positive Symptoms (SAPS), the Scale for the Assessment of Negative Symptoms (SANS), the

Hamilton Depression Rating Scale (HDRS), the Bech-Rafaelsen Manic Rating Scale, the 7-point Clinical Global Impression (CGI) Scale, the Global Assessment Functioning (GAF), Auditory Hallucinations Rating Scale (AHRS), and Specific Level of Functioning Scale (SLOF).

Sub Study:
Psychopathological ratings listed above will be completed at the 1 week time point and 2 month time point.

Medical assessments
A medical history will be obtained on all participants.

Experimental Procedures: tDCS, EEG, MRI

tDCS
tDCS intervention consists of two daily sessions, separated by 1 hour, over 5 consecutive days. Such strategy is commonly used in clinical studies, yielding prolonged clinical effects while being well-tolerated. Electrical stimulation will be delivered by a constant-current multi-channel stimulator (NeuroMod tXES Stimulator, RGN, New Mexico, USA) through conductive-rubber electrodes placed in sponges saturated with saline (0.9% NaCl). As per schematic in the figure inlay, left DLPFC will be targeted positioning the anode electrode midway between F3 and FP1 location of the 10-20 system. The cathode electrode will be positioned over left TPJ, midway between T3 and P3.

Patients in the treatment group will receive 20 min of 2 mA direct current stimulation with 20 sec fade in/out. The Sham group will undergo exactly the same procedures but stimulation (aside from the initial and last 20 seconds) will consist of brief (1 sec) low current (.11 mA) pulses every 10 sec.

Sub Study:
All subjects in the sub study will receive the active treatment consisting of 20 min of 2 mA direct current stimulation with 20 sec fade in and fade out.

Safety and tolerability assessment
The stimulation strategy and the electrode montage used in the present studies are commonly reported as well tolerated.

The risks to subjects related to receiving tDCS are minimal and confined to discomfort, such as itching and tingling on the scalp (Brunoni et al. 2011). However in rare instances, some participants may experience the stimulation as a stinging sensation that is uncomfortable. Very rarely, there may be heating and even burning of skin. Skin lesions do not occur with modern microchip controlled stimulators, accordingly the NeuroMod tXES stimulator meets the highest safety standards by micro-processor-controlled current outflow with multistage monitoring of the impedance. As discomforting sensations are more often reported when current is abruptly started or stopped, active current levels will be achieved by slowly ramping up current from zero and the stimulation will be interrupted trough fading it out. Periodically subjects will be actively required to provide a feedback about their degree of comfort and they will be able to speak with experimenters at all time. Subjects will also be asked to rate their pain from 0 to 10 (11 point scale) using a numerical rating scale (NRS) for a standardized assessment of pain. Literature suggests compliance at high tolerability for the used current levels. In the rare event of subject reporting the stimulation highly discomforting or intolerable, the stimulation will be promptly stopped. If the subject is unwilling to resume the protocol, he/she will be drop out from the study. In addition, we will collect a tDCS adverse event screening questionnaire. The questionnaire will be administered after the first session of tDCS and again at the last tDCS session. Participants will have the option to apply topical lidocaine on the scalp 20 minutes prior to tDCS in order to minimize the chance of uncomfortable stimulation. This will likely reduce the possibility of participants dropping out of the study who may be more sensitive to the stimulation.

Cognitive testing and EEG

Cognitive effects will be evaluated the day prior and one week after the first tDCS session to assess acute effects compared to baseline, and two months later to evaluate their persistence. Immediate effects after the first tDCS application will also be investigated in order to explore early response predictors.

Subjects will be asked to do some simple tasks which will involve looking at a computer screen display (figures, symbols, numbers, letters, words or sentences) or listening to sounds through headphones (clicks, beeps, or words). The participant is asked to respond to the stimuli by pressing a response button. Stimuli will be presented on a computer screen using E-Prime (Psychological Software Tools, Pittsburgh, PA). Dependent variables will be reaction time, response, and accuracy collected via keyboard, joystick, button box or similar device and stored on a computer. The task will involve separate trials and trials are organized in blocks so that participants will be allowed to rest in between blocks. In each session, cognitive tasks will be presented on a computer screening using E-Prime (Psychology Software Tools, Pittsburgh, PA). EEG will be administered with concurrent high- density (64 channel EEG acquisition (BrainAmp MRPlus, Brain Products, Munich, Germany) system. This system is CE certified.

Sub Study:
Cognitive testing and EEG will be completed on the 1st day of tDCS, the 1 week time point, and the 2 month time point.

Safety and tolerability assessment

The Electroencephalography (EEG) system is not FDA approved, but CE certified. It is a non-invasive procedure which may cause skin irritation from the placement of recording electrodes in less than 1% of people. Itchiness of scalp or redness because of electrode gel could result and has the same amount of risk as saline solution. The EEG is administered by trained research staff and can be stopped at any time if the subject becomes uncomfortable.

MRI

Subjects within the first 5 years of antipsychotic treatment will undergo MRI in order to assist localization of EEG data and provide independent and complementary correlates of tDCS effects. A technician will place the head-coil on the subject, which is like wearing a helmet. The subject will be asked position themselves on a platform that slides inside a large tube (the MRI machine). The subject will be asked to perform computer tasks while in the MRI scanner. These tasks maybe similar in nature to the ones performed during EEG. Participant will be given specific instructions before the session and again for each task before it begins. MRI sequences will involve full brain scans - high-resolution structural T1 weighted sequence and functional EPI - and focal spectroscopy focused on a 2cm isotropic voxel within left DLPFC. Resting state fMRI and DTI may also be acquired. Functional Magnetic Resonance Spectroscopy (MRS) may also be acquired. The scanning session will include both functional and structural MR images.

Sub Study:
The sub study will not include MRI procedures.

Safety and tolerability assessment

MRI is very safe, with no radiation or contrast media involved. The procedure has the same risk as a clinical MRI. The only risks of the procedure would be in the event that the patients have metal particles in their body, which if mobile could act as projectiles, or be mechanically activated or displaced if implants. These risks will be minimized using systematic procedures and well-trained technicians, with very careful screening for metal and implants prior to scanning. Claustrophobic reactions can make participation impossible for some subjects. History suggesting of a predisposition will be investigated. However discomfort could arise within the bore even in absence of positive history. The technician will make sure the individual is comfortable before starting the imaging. During the MRI, the subject will hold onto a ball that sounds an alarm when squeezed and will be

instructed to do so if he/she becomes uncomfortable during the procedure. If that happens, the technician will stop the scan to check on the participant.

Further Safety Issues
Another potential risk is the possibility of loss of confidentiality in case information is lost or misplaced. All PHI will be kept in locked drawers or password protected storage on computers.

Any unanticipated problems will be reported to IRB immediately (within 24 hours). The research team will meet on a weekly basis to review study safety issues, adverse events, data integrity and any other relevant study issues. Any significant concerns or issues during the conduct of the study will be immediately communicated to the study PI.

Data Analysis
Ratings, behavioral and neurophysiological variables will enter GLM to assess interactions of group (treatment vs sham) and time points, with planned contrasts to index size effects and trajectories. On the basis of the reported studies, our experience with the population, relatively short study duration and good overlap of the two arms conditions, we expect only minimal occurrence of data missing at random. EEG analysis will be conducted with in house MATLAB scripts and will mainly focused on time-frequency analysis for modulation of power by experimental factors (CC and WM load) and to extract phase information in order to perform phase-amplitude cross-frequency coupling analysis. Beamforming source localization will be using Fieldtrip (Nijmegen, NL). fMRI analysis will be conducted in the FSL framework (FSL, Oxford,UK). MRS analysis will be performed using the jMRUI software package version 2.2 (http://www.mrui.uab.es/mrui).

Regulatory Ethics Compliance

Investigator Responsibilities
The investigator is responsible for ensuring the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice, and applicable regulatory requirements. During the study the investigator will send the following documents and updates to the Baylor College of Medicine Institutional Review Board for their review and approval, where appropriate:

a) Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study contact)

b) Revision(s) to ICF and any other written materials to be provided to subjects.

c) Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable.

d) Reports of adverse events that are serious, unlisted/unexpected, and associated with the study protocol.

e) Deviations from or changes to the protocol to eliminate immediate hazards to the subjects.

f) Any other requirements of the IRB.

At the end of the study, the investigator will notify the IRB about the study completion.

Informed Consent
Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF will be signed before performance of any study-related activity. The ICF that is used must be approved by the reviewing IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles with current ICH and GCP guidelines and applicable

regulatory requirements. Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease.

The subject will be given sufficient time to read the ICF and the opportunity to ask any questions. After having obtained written consent, a copy of the ICF will be provided to the participant.

IRB approval will be sought from Baylor College of Medicine Institutional Review Board. Privacy and confidentiality will be maintained with a special number to be used to identify the subject in the study and only the investigator and his research staff will know their name.

Data handling and record keeping

Procedure for maintaining subject confidentiality

The clinical information obtained from subjects will be part of their study records and maintained at BCM in a facility with adequate safeguards for the protection of confidentiality. The research data will be collected and recorded using only arbitrary study IDs. All data will be kept in a secure area. Only the members of the research group will have access to the data files or to the master list for the codes (linking log form attached). For publication purposes, the patients will be designated only by codes. Our research team is in compliance with all HIPAA privacy guidelines. In summary, the potential risks for participants in this study will be minimized by careful medical and psychiatric evaluations and procedures, regular monitoring of subjects' clinical status, careful screening of subjects before the EEG and MRI scans and defined procedures for maintaining confidentiality.

Quality control and assurance

No plans to have ongoing third party monitoring. However, we will conduct routine (bimonthly) reviews of consistency, reliability and accuracy of data collected for any paper records. Similar checks for any data in electronic form will also be conducted but in an automated fashion (e.g checking for accurate time/date stamps, file sizes etc.). We also have a DSMB that will meet after every 10 participants have enrolled and completed their study visits. The DSMB will periodically assess data quality along with the other responsibilities listed in their charter.

Publication Plan

We plan to present preliminary versions of the findings at conferences during the first and second year. Definitive publication of findings will occur in the 6-12 months following the end of the two-year award period.

References

1. Brunelin M, et al Examining Transcranial Direct-Current Stimulation (tDCS) as a Treatment for Hallucinations in Schizophrenia. Am J Psychiatry. 2012 169(7), 719–724.
2. Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, Edwards DJ, Valero-Cabre A, Rotenberg A, Pascual-Leone A, Ferrucci R, Priori A, Boggio PS, Fregni F. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul. 2012 Jul; 5(3):175-95.
3. Cho RY, Konecky RO, Carter CS. Impairments in frontal cortical gamma synchrony and cognitive control in schizophrenia. Proc Natl Acad Sci U S A. 2006 Dec 26; 103(52):19878-83
4. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? AmJ Psychiatry. 1996 Mar; 153(3):321-30
5. Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci.2005; 6:312–324.
6. Lisman J, Buzsaki G. A neural coding scheme formed by the combined function of gamma and theta oscillations. Schizophr Bull. 2008;34:974–980
7. Mondino M, Brunelin J, Palm U, Brunoni AR, Poulet E, Fecteau S.Transcranial Direct Current Stimulation for the Treatment of Refractory Symptoms of Schizophrenia. Current Evidence and Future Directions. Curr Pharm Des. 2015; 21(23):3373-83.
8. Stagg CJ, Best JG, Stephenson MC, O'Shea J, Wylezinska M, Kincses ZT, Morris PG, Matthews PM, Johansen-Berg H. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J Neurosci. 2009 Apr 22; 29(16):5202-6.
9. Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. Neuroscientist. 2011 Feb; 17(1):37-53.
10. Uhlhaas PJ, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. Nat Rev Neurosci. 2010 Feb; 11(2):100-13
11. Volk DW, Lewis DA. Prefrontal cortical circuits in schizophrenia. Curr Top Behav Neurosci.2010; 4:485-508.