FULL PROTOCOL TITLE

Neuromodulation plus cognitive training to improve working memory among individuals with serious mental illness

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Protocol Summary

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Abstract:

***Background*:** People with serious mental illness (bipolar disorder and schizophrenia-spectrum illness) often demonstrate impaired neurocognition; in particular, working memory has been proposed as a shared neurocognitive endophenotype of these disorders. Novel non-pharmacological treatments have shown promise, with some evidence that cognitive remediation confers benefit in terms of neurocognitive symptoms and functional performance. The published effect sizes, however, are somewhat modest, prompting researchers to focus on potential "cognitive enhancers" to boost the effects of training. Neuromodulation, specifically transcranial direct current stimulation (tDCS), is one potential enhancing treatment that is considered exceptionally safe and cost-effective.

***Study Design*:** The proposed study aims to investigate the feasibility, acceptability, and initial efficacy of a combined computerized cognitive training and tDCS intervention, using a randomized sham-controlled design including individuals with serious mental illness. This study is a critical first step in advancing the evidence-base regarding treatments that can improve neurocognitive abilities and functional outcome among those affected by psychiatric illness. Examining whether tDCS is a realistic treatment option for individuals with psychiatric illness, and whether adding tDCS to a cognitive training paradigm improves working memory performance beyond the positive effects of training alone, will lay the groundwork for additional investigation with larger samples.

Objectives: 1) determine the feasibility and acceptability of tDCS treatment and computerized cognitive training in this population; 2) examine preliminary efficacy of the combined treatment on main outcome: working memory performance.

Population: Patients aged 18-65 diagnosed with schizophrenia, schizoaffective disorder, or bipolar disorder
Site: University of Michigan
Study Duration: 2 years
Participant Participation Duration: 2 months
Study Design: Randomized controlled trial
Number of participants: 12 completers for Aim 1, 30 completers for Aim 2, 1:1 randomization
Description of Intervention: 2mA stimulation to left dorsolateral prefrontal cortex, 10 treatment sessions; 10 hours of computerized cognitive training
Estimated Time to Complete Enrollment: 2 years

1.0 Background and Significance

Neurocognitive impairment is prevalent among individuals with serious mental illness (SMI; bipolar disorder and schizophrenia-spectrum disorders), and is associated with functional disability beyond the effects of symptoms alone. Although the magnitude of deficits is typically greater amongst people with psychotic illness, the pattern is similar across categorical SMI diagnoses and may represent a dimensional, cross-diagnostic feature of those affected by SMI[1-4]. Among other neurocognitive domains, working memory is commonly impaired in both bipolar disorder and schizophrenia, with some evidence that it represents a shared neurocognitive endophenotype among individuals with SMI[5,6]. A burgeoning area of research involves neuroplasticity-based treatment called cognitive remediation (also known as cognitive training), defined as "a behavioral training-based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition or metacognition) with the goal of durability and generalization"[7]. The current evidence generally supports the efficacy of cognitive remediation in mood disorders as well as schizophrenia[7,8]. However, a broad array of training techniques has been reported in the literature, all of which appear to demonstrate some efficacy but none of which emerge as clearly superior. Therefore, there is a growing emphasis on applying novel techniques in conjunction with remediation paradigms; for example, via a "cognitive enhancer" like transcranial direct current stimulation (tDCS) to boost the effects of cognitive training.

In the context of SMI, tDCS has been identified as a promising treatment to reduce depressive symptoms among individuals with bipolar depression, although not all trials have shown significant benefits[9,10]. There is also some limited evidence that tDCS may be effective in treating auditory hallucinations and possibly improving cognitive functioning among people with schizophrenia[11], although to date most published works were case studies, used single tDCS sessions, or did not include cognitive training concurrent with stimulation. Researchers have concluded that there is potential utility in use of tDCS for cognitive remediation, and have identified the use of tDCS as monotherapy or in combination with cognitive training as an area of future emphasis[11].

The proposed study is a critical first step toward a larger RCT, aiming to collect preliminary pilot data on the feasibility, acceptability, and initial efficacy of a combined neuromodulation and cognitive training intervention for individuals with SMI. Thirty participants diagnosed with SMI will be enrolled; participants will be randomized to receive 10 sessions of either active or sham tDCS, and will concurrently complete 10 hours of computerized cognitive training focused specifically on working memory abilities.

2.0 Specific Aims and Study Outcome Measures

2.1 Specific Aims

Specific Aim 1: Determine the feasibility and acceptability of delivering a combined neuromodulation (tDCS) plus cognitive training intervention to outpatients with SMI (n=12). Individuals with SMI, particularly those with neurocognitive impairment, often face barriers to treatment access and retention. The proposed study will incorporate various strategies to support participant retention and promote acceptability, with the hypothesis that participants will be able to tolerate 10, 20-minute sessions of tDCS in the clinic and 10 hours of computerized cognitive training over the course of 4-8 weeks.

****NOTE: Aim 1 corresponds to NCT03338673 registered on clinicaltrials.gov. ****

Specific Aim 2: Collect pilot data on the efficacy of the combined intervention, comparing neurocognitive performance following active tDCS treatment to performance after cognitive training alone (sham tDCS). The proposed analyses will test the hypothesis that active tDCS plus computerized cognitive training will produce a synergistic effect, where performance following the combined treatment will be superior to performance following sham stimulation/cognitive training alone.

****NOTE: Aim 2 is registered on clinicaltrials.gov as NCT05111548****

2.2 Study Outcome Measures

Aim 1: Determine the feasibility and acceptability of delivering a combined neuromodulation (tDCS) plus cognitive training intervention to outpatients with SMI.

Primary outcome: Participant retention, defined as the percentage of enrolled participants who complete the combined intervention.

Secondary outcome: Self-reported treatment satisfaction, as measured on a 1-10 scale at study completion.

Aim 2: Collect pilot data on the efficacy of the combined intervention, comparing neurocognitive performance following combined treatment to performance after cognitive training alone.

Primary outcome: change in working memory performance

Secondary outcome: change in non-working memory comparison measures

3.0 Study Design

3.1 Overview of Experimental Design

Aim 1 (feasibility and acceptability) will include a randomized crossover design, where all 12 participants will receive both the combined intervention (active tDCS plus BrainHQ computerized cognitive training), and computerized cognitive training alone, with starting condition randomly determined. Aim 2 (efficacy) will be a randomized, controlled trial, where half of the participants (n=15) will be randomized to receive active transcranial direct current stimulation (tDCS) plus BrainHQ computerized cognitive training, and half (n=15) will receive sham tDCS plus BrainHQ computerized cognitive training (Table 1). Participants will attend 10 treatment sessions in the clinic. If able to attend daily, participants will complete these sessions in 2 weeks; to allow for unanticipated absences or difficulty with attendance, up to 4 weeks will be permitted for completion. Following completion of these 10 treatment sessions, participants will return after one month of no study contact to complete a follow-up assessment.

3.2 Interventions

Cognitive training: Software licenses for a commercially-available computerized cognitive training package titled BrainHQ will be purchased and provided to each participant (http://www.brainhq.com/). To date, more than 30 published manuscripts and abstracts reported on the effects of BrainHQ for individuals with SMI; it also meets each of the 5 criteria recently published by the Institute of Medicine in support of a brain-training program's scientific merit. This program offers a variety of working memory-specific training paradigms, individualized feedback and progress notification, and administrative oversight of training exercises as well as detailed usage reports. BrainHQ can be accessed from any web-enabled computer and has both tablet and mobile applications available on Apple devices.

tDCS: There are data suggesting that tDCS can affect functioning in the prefrontal cortex, an area often implicated in models of neurocognitive dysfunction. In particular, stimulation of the dorsolateral prefrontal cortex (DLPFC) is commonly used; this functional region is believed to underlie executive cognitive functions like working memory and cognitive flexibility, which are popular targets of cognitive training interventions. Because there is no clear guide from the literature on (1) location of electrode placement, (2) frequency of stimulation, or (3) duration of stimulation, the montage and procedures proposed here are guided by the general consensus in the published literature, hypothesized neural circuitry of interest, and what is presumed to be most acceptable to participants. Based on these features, the anticipated montage will include concurrent anodal (excitatory) stimulation of 2 mA over the left dorsolateral prefrontal cortex, and cathodal (inhibitory) stimulation over right dorsolateral prefrontal cortex, over a total of 10 sessions lasting 20 minutes each. Minor deviations are possible but are not expected to significantly increase risk to participants. For example, as new data emerge, we may shift the montage, e.g. cathodal stimulation to parietal region. Participants will complete BrainHQ exercises concurrently during stimulation. All treatment sessions will take place at the Rachel Upjohn Building (RUB).

3.3 Procedures

Participants will include a total of 42 individuals who are self- or clinician-referred in response to advertisements posted in Ambulatory Psychiatry/RUB or in the community. Participants may also be recruited from the Prechter Bipolar Longitudinal Study or Dr. Tso & Taylor's studies. Enrollment will occur on a rolling basis, with anticipated enrollment of 1-2 participants per month. Potential participants will

meet with a study coordinator to provide written informed consent; following consent, participants will complete a structured diagnostic interview to confirm eligibility; participants not meeting the inclusion criterion (below) will be compensated for their time and excluded from further participation. To minimize attrition and missing data, participants will be compensated for each visit (up to $200 total); study staff will also provide reminder phone calls for appointments, and may arrange transportation via cab if and when possible.

3.4 Schematic

Aim 1.

<table>
<tr><th></th><th>Week 0</th><th>Weeks 1-4</th><th>End of Week 4</th><th>Weeks 5-8</th><th>Week 8</th></tr>
<tr><td>Group A
(6 participants)</td><td rowspan="2">Baseline assessment</td><td>tDCS + BrainHQ</td><td rowspan="2">Mid-point assessment</td><td>BrainHQ</td><td rowspan="2">Post-treatment assessment</td></tr>
<tr><td>Group B
(6 participants)</td><td>BrainHQ</td><td>tDCS + BrainHQ</td></tr>
</table>

Aim 2.

<table>
<tr><th></th><th>Week 0</th><th>Weeks 1-4</th><th>End of Week 4</th><th>Weeks 5-8</th><th>Week 8</th></tr>
<tr><td>Group A
(15 participants)</td><td rowspan="2">Baseline assessment</td><td>Active tDCS + BrainHQ</td><td rowspan="2">Post-treatment assessment</td><td rowspan="2">No contact</td><td rowspan="2">Follow-up assessment</td></tr>
<tr><td>Group B
(15 participants)</td><td>Sham tDCS + BrainHQ</td></tr>
</table>

4.0 Study Participants

4.1 Inclusion Criteria

(1) age 18-65, (2) diagnosis of bipolar disorder I or II, schizoaffective disorder, or schizophrenia, as confirmed by structured diagnostic interview, and (3) willingness to complete computerized cognitive training and undergo brain stimulation procedures.

4.2 Exclusion Criteria

(1) history of neurological illness or brain injury (e.g., stroke), (2) history of loss of consciousness > 20 minutes, (3) diagnosed intellectual disability, (4) current (i.e., past 30 days) substance use disorder, (5) current mania (YMRS ≥ 10) or moderate depression (HAM-D ≥ 17) or severe psychosis (PANSS positive symptom total ≥ 35), (6) serious suicidal ideation/behavior (endorse questions 4 or 5 or suicide behaviors within the past 3 months, according to the C-SSRS), (7) pregnant or trying to become pregnant, or currently lactating, (8) presence of metal (except titanium) or electrical implants in the brain or skull (e.g., surgical clips, deep brain stimulator, cochlear implants, splinters/fragments, skull plate), (9) presence of implanted medical devices elsewhere in the body (e.g., cardiac pacemaker or medical pump).

4.3 Strategies for Recruitment and Retention

Recruitment will be from the outpatient psychiatry programs at the University of Michigan Health System, from flyer advertisements, and by clinician referral. The recruitment process is designed to limit interference with clinical care and assure the informed participation of patient participants. By obtaining a waiver of consent for screening purposes, recruitment is facilitated by pre-review of computer-based medical records to identify potential research participants who have contacted the Department of Psychiatry. In addition, we will scan umhealthresearch.org, the UM registry of individuals who are interested in participating in health research. Study coordinators will make contact with clinic staff to interview patients who express an interest in a study, or who appear eligible based on initial review of electronic records. For all patients who are screened for the study, we will contact their clinician, if not already done during pre-screening (psychiatrist and/or psychotherapist), notify them of their patient's interest and verify that the participant is eligible to participate. The patient's clinician(s) will also be notified via a memo when the patient has enrolled and is scheduled for the study treatment.

4.4 Treatment Assignment Procedures

4.4.1 Randomization Procedures

Following baseline assessment, participants will be randomized to complete either the combined treatment (active tDCS plus cognitive training) or cognitive training alone (sham tDCS). Participants and clinical assessors will be blinded to condition; at the post-treatment assessment visit, participants and the assessor will guess group assignment to evaluate how well the blind was maintained.

4.4.2 Reasons for Withdrawal

During the pre-screening process, participants who are found to be non-eligible, before formal signing of a consent form, will be considered *not enrolled*, and all data related to that participant will be destroyed. Participants who consent, and are found not eligible during the assessment and screening will be considered *screen failures*, and all research and identifying data will be destroyed, except for the consent form and limited information to document the screen failure (age, gender, diagnosis, specific reason for exclusion). Participants who leave the study after signing the informed consent, and after being deemed eligible/enrolled/randomized, will be considered *withdrawn*. Participants may withdraw from the study at any time and for any reason. Participants may be withdrawn by the investigator when continued participation would present an unacceptable risk to the participant. This would include, but is not limited to, significant adverse events related to the device, (e. g., intolerable discomfort), or participants who experience severe symptom worsening, including suicidal thoughts or behaviors, which require hospitalization.

4.4.3 Handling of Withdrawals

If a participant wishes to withdraw from the study and all assessments, his/her intention will be honored. For withdrawn participants, data will be retained and used at the discretion of the investigator.

4.4.4 Termination of Study

This study may be prematurely terminated if, in the opinion of the investigator or the sponsor, there is sufficient reasonable cause. Written notification, documenting the reason for study termination, will be provided to the investigator or sponsor by the terminating party. Circumstances that may warrant termination include, but are not limited to: determination of unexpected, significant, or unacceptable risk to participants; insufficient adherence to protocol requirements; data that are not sufficiently complete and/or evaluable. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason for the termination or suspension.

4.5 Pre-Screening

Potential participants will be screened informally, usually over the telephone, possibly face-to-face (see pre-screening form) in order to make a preliminary assessment of their eligibility. Patients who appear eligible and express interest in participating will be scheduled for a screening/assessment visit.

5.0 Study Schedule

5.1 Screening and Initial Assessment Visit

5.1.1 Informed Consent

The session will begin by having the participant provide written informed consent. Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of these treatments will be provided to the participants and any family members or others the participant would like to include in the process. Consent forms (written in non-technical language) describing in detail the study interventions/products, study procedures, and risks will be given to the participant and written documentation of informed consent is required prior to starting the intervention. Consent forms will be IRB-approved and the participant will be asked to read and review the document. Upon reviewing the document, the investigator (or her designee) will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate.

Participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

5.1.2 Initial Assessments

This session will continue with completion of a brief demographic questionnaire and clinical measures to confirm eligibility and characterize current symptoms. These include:

1. Mini-International Neuropsychiatric Interview (MINI), a short structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders
2. Hamilton Depression Rating Scale (HAM-D)
3. Young Mania Rating Scale (YMRS)
4. Positive and Negative Syndrome Scale (PANSS)
5. Columbia Suicide Severity Rating Scale (C-SSRS)

Note. To allow for maximal appropriate distancing owing to the ongoing COVID-19 pandemic, these interview-based clinical measures may be completed virtually while the participant is physically in the building and the clinician is in a remote location, via a secure and approved telehealth platform (Zoom for Health). Because the participant will be in the clinic with another study staff member (who will be administering the informed consent and the portion of the assessment that requires manipulation of materials), there are no anticipated changes to safety or risk-assessment protocols. Any safety concerns will be immediately communicated between the study clinician and research assistant, and appropriate action will be taken (see section 5.5.1).

Neuropsychological and functional measures will also be administered to characterize current neurocognitive functioning. These include:

1. Wide Range Achievement Test, reading subtest (WRAT-4)
2. MCCB: Trails A, letter-number span, spatial span
3. Trails B
4. Specific Levels of Functioning (SLOF) clinician-rated questionnaire

This screening and initial assessment visit is expected to last up to 2.5 hours.

5.2 tDCS Treatment visits

5.2.1 Overview

tDCS traditionally uses two electrodes (an anode and a cathode) that are placed according to the international 10-20 system (or the extended 10-20 system), allowing for easy replication both within and across studies. The neurons underlying the anode become depolarized (“excited”) whereas those underlying the cathode become hyperpolarized (“inhibited”). A study team member will be present in the room with the participant during the stimulation session. tDCS is administered while the participant sits in a chair. Following placement of the electrodes, either active or sham tDCS will commence: in both conditions, a brief ramp up period will occur first in which the electrical current is gradually increased. In the active condition, the current will reach 2mA and will be sustained at that level for 20 minutes, then a ramp down period will take place during which the current is gradually removed. The sham condition mirrors the ramp up and ramp down of active stimulation but does not otherwise deliver a current. The proposed montage includes anodal (excitatory) stimulation over the left dorsolateral prefrontal cortex, and cathodal (inhibitory) stimulation over right dorsolateral prefrontal cortex. The exact duration, frequency and amount of stimulation may vary from these procedures based on feedback from participants (but will not exceed 2 mA or 20 minutes), so the parameters will always fall within the safety guidelines. For example, if a participant reports discomfort, stimulation will be paused and additional saline/gel will be added to improve the contact (i.e., reduce resistance), or the current will be incrementally reduced to a tolerable level. The participant will concurrently complete BrainHQ working memory exercises during and immediately after the stimulation session, for approximately 60 minutes total. Treatment will occur in a designated room on the second floor of the Rachel Upjohn Building, department of Psychiatry.

5.2.2 Treatment Device

A Soterix Clinical Trial (CT) stimulator will be used. The unit is powered by standard 9v batteries and has a number of built-in safety features that limit the maximum possible current to the programmed parameters. The unit includes a switch to select active or sham stimulation. This unit is considered an investigational device by the FDA. Based on the scientific literature available to date, this device is believed to be of non-significant risk (NSR).

5.2.3 Stopping Rules

In the event that a participant reports discomfort during the tDCS procedure, stimulation will be paused and additional saline/gel will be added to improve the contact, or the current will be incrementally reduced. The session will be discontinued if the patient reports continued discomfort. Immediately after each stimulation session ends, participants will complete a tDCS side effects questionnaire. A study team member will review the responses and will immediately consult the PI if a participant reports a moderate-severe rating for any of the side effects. Those participants, if any, will be given the option of withdrawing from the study. The PI will also withdraw participants if the nature of the side effect is unusual (i.e., not listed as a common side effect) or concerning (e.g., significant acute mood change). Clinically trained study staff will monitor participants closely for mood changes and/or any emergence of suicidal ideation throughout the duration of participation. Participants will be withdrawn in the event of significant symptomatic worsening, including:

1. Current mania: YMRS change of ≥ 7 points at mid-point assessment or clinical observation indicating current mania
2. Worsening of depressive symptoms: 25% increase (i.e., greater severity) in HAM-D total score at mid-point assessment
3. Worsening of psychosis: 25% increase (i.e., greater severity) in PANSS positive total score at mid-point assessment
4. Suicide risk evaluated by a clinician to be high and imminent (e.g., current suicide plan and intent)

5.2.4 Early Termination Assessments

If early termination occurs and, if the participant is willing and able, all of the outcomes and safety assessments noted above for the final experimental visit will be performed.

5.3 Computerized cognitive training

Participants will be provided a personalized login to the BrainHQ website and provided a tutorial to orient them to the training program. They will complete a total of 10 hours of working memory exercises specifically, as selected and monitored by the study team. BrainHQ can be accessed online on a desktop computer, laptop, Apple tablet, or Apple mobile phone. In the event that a participant does not have reliable access to one of these devices, arrangements will be made to complete training on an available computer at RUB.

5.4 Subsequent assessment visits (post-treatment and follow-up)

Participants will complete follow-up assessments at the conclusion of treatment (post-treatment) and at one-month follow-up. Measures will include:

1. Hamilton Depression Rating Scale (HAM-D)
2. Young Mania Rating Scale (YMRS)
3. Positive and Negative Syndrome Scale (PANSS)
4. MCCB: Trails A, letter-number span, spatial span
5. Trails B
6. Specific Levels of Functioning (SLOF) clinician-rated questionnaire

These visits are expected to last up to 1.5 hours.

5.5 Assessments

Participants will complete assessments at three time points: baseline (pre-treatment), post-treatment, and follow-up.

Assessment schedule and administration time requirements.

	Baseline	Post-treatment	Follow-up	Administration time (mins)
Clinical measures				
MINI diagnostic interview	x			60
HAM-D, YMRS, PANSS	x	x	x	15-30
C-SSRS	x			5
Neuropsychological measures				
WRAT reading	x			5
MCCB (Trails A*; letter-number span; spatial span)	x	x	x	30
Trails B*	x	x	x	5
Functional measures				
SLOF	x	x	x	10
Total estimated time	≤ 2.5 hours	≤ 1.5 hours	≤ 1.5 hours	

*Trails A and B will be administered as non-working memory neurocognitive comparison measures

5.5.1 Assessment of Suicidality

For any potential participant who reports concerning suicidal thoughts/behaviors (defined according to the MINI, HAM-D, or C-SSRS), the PI will be notified and a further risk assessment of the patient will be conducted, including the identification of risk factors (e.g., substance abuse, active psychosis, hopelessness), mitigating factors (e.g., social support, degree of control over suicidal thoughts, religious beliefs against suicide) and the level of suicidal ideation/behavior. An intervention plan will be formulated, taking into account the level of risk and treatment resources available to the potential participant. This could include monitoring by family, contact with a treating clinician (with the patient's permission), follow-up phone calls, or urgent evaluation in the psychiatric emergency room. For individuals without a treating clinician, referrals to available community resources will be made.

5.6 Concurrent care

Participants may continue to see their current mental health clinicians through the course of the trial in order to minimize disruption in existing treatment. Communication with the treating provider(s) will be made prior to the onset of treatment with the participant's knowledge and permission.

5.7 Payment of participants

Participants will be compensated for each assessment visit, with increasing amounts to promote retention and study completion. Participants will receive $20 for completing the baseline assessment, $30 for completing the post-treatment assessment, and $50 for completing the follow-up assessment, for a total of $100 per participant. To offset transportation costs and promote treatment retention, participants will be compensated $10 for each tDCS clinic visit, for a total of $100 per participant. The total compensation per participant is $200.

6.0 Assessment of Safety and Regulatory Reporting

6.1 Data Safety and Management Plan

6.1.1 Data Management

Research data will be maintained on password protected computers, behind UM firewalls. All enrolled participants will receive participant identifiers, which will be used to code all research records for this project. Paper records with no identifying data beyond the research code are stored in locked cabinets in the PI's office. Copies of executed consent forms will be stored in separate locked cabinets. Demographic data will be entered into spreadsheets, and behavioral data will be merged into files. Password-protected electronic files separated from the research data will track consents, including the link between the research identifier and individual participants. This tracking file will be the sole link

between participant identifiers and research data. By deleting the field linking identifiers with participant names, research records can be effectively anonymized.

6.1.2 Management of withdrawals and drop-outs

Procedures for these events are described in sections 4.4.2, 4.4.3, and 4.4.4.

6.1.3 Adverse Events (AEs)

An AE is defined as any untoward occurrence in a patient or clinical investigation participant administered an intervention regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the intervention. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. At each treatment session participants will be questioned about putative AEs. Information to be collected includes event description, time of onset, clinician's assessment of severity (mild, moderate, or severe), relationship to study product (assessed by the study clinician, Dr. Burton), expected versus unexpected, local versus systemic, and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution. Adverse event reporting will occur on the standard IRBMED timetable.

6.1.4 Serious Adverse Events (SAEs)

An SAE is defined as an AE that meets one of the following conditions:

Death during the period of protocol-defined surveillance

Life-threatening event (i.e., a participant at immediate risk of death at the time of the event)

An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance

Results in congenital anomaly or birth defect

Results in a persistent or significant disability/incapacity

Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse/overdose or cancer.

All SAEs will be:

- Followed through resolution by a study clinician
- Reviewed and evaluated by a study clinician
- Reported to Soterix, the company supplying the tDCS unit to the investigators

The study will comply with IRB and FDA reporting requirements and guidelines for SAEs.

6.1.5 Unanticipated Problems

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (in the guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and suggests that the research places participants or others at a greater risk of harm (including

physical, psychological, economic, or social harm) than was previously known or recognized.

- An incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in order to protect the safety, welfare, or rights of participants or others.

Unanticipated problems will be recorded and reported throughout the study.

6.2 Event Windows, Missed Assessments/Sessions and Protocol Deviation Reporting

For the post-treatment and follow-up assessments, a window of ± 10 days will be permitted (not including weekends). Any safety-related assessments (HAM-D, YMRS, PANSS, C-SSRS) or primary outcome measure (MCCB working memory) which are missed or obtained outside the window will be reported to the IRB as a protocol deviation. However, for the other assessments, missing or late assessments will not be reported as protocol deviations unless they constitute > 10% of the total assessments. In order to accommodate inevitable scheduling conflicts, holidays, etc., participants will be allowed to complete the 10 tDCS sessions within 4 weeks. Participants who do not complete all 10 tDCS sessions or all 10 hours of cognitive training will be retained in the study and their outcome data will be compared to those participants who completed the full course of treatment. These allowances should affect neither the scientific integrity nor the safety monitoring provisions of the protocol.

7.0 Clinical Monitoring

The investigators will meet weekly (as close to that as permitted by travel and holidays) to monitor the study activities to ensure that the human participant protection, study procedures, administration, and data collection processes are of high quality and meet the appropriate, regulatory guidelines.

Standard monitoring procedures in place for tDCS therapy will be followed for this protocol. During tDCS therapy, operators are trained to monitor patients for any side effects. If a participant reports side effects, these are noted and dealt with according to severity. Importantly, tDCS does not directly induce neuronal firing and there has never been a reported case of tDCS induced seizure.

8.0 Statistical Analysis

8.1 Data Analysis

Specific Aim 1: Feasibility will be evaluated through participant retention, and will be calculated as the percentage of enrolled participants who complete the combined intervention. Acceptability will be evaluated by participant-rated satisfaction with the intervention, as rated on a 1-10 scale (where 1 is low satisfaction and 10 is high) collected at study completion.

Specific Aim 2: Mixed-factorial ANOVA will be used to examine between-group (Group A: active tDCS, versus Group B: sham tDCS) and within-group (time) effects on the main outcome measures: MCCB letter-number span score and MCCB spatial span score. Mean performance for each group at each time point will be plotted and examined.

9.0 Source Documentation

Medical and research records will be maintained to ensure the protection of confidentiality of participants (see section 12). Only study staff will have access to these records.

10.0 Quality Control and Assurance:

The PI will review data collection and entry periodically to evaluate compliance with the protocol and for accuracy.

11.0 Ethics and Protection of Human Participants

11.1 Ethical Standard and IRB review

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Participants of Research, as drafted by the US National Commission for the Protection of Human Participants of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997) and the Declaration of Helsinki and Good Clinical Practice (GCP). All protocol amendments must be IRB approved prior to implementing, except when change is for patient safety.

11.2 Participant Confidentiality

11.2.1 Measures to protect patient privacy

Study staff will make every effort to limit identifiable information on potential participants during recruitment. Conversations in which a patient's name must be mentioned (e.g., to determine potential eligibility), will occur in private settings of the clinic. The minimum amount of information will be recorded, and staff will be alerted to the dangers of printing, faxing and emailing sensitive information. Phone conversations with potential research participants will occur behind closed doors, and staff will ask callers if they are in a location where sensitive information can be discussed without danger of revealing confidential information. Any information gathered on participants who prove ineligible will be destroyed as soon as possible (a list of patients who have declined or screened out will be maintained through the recruitment phase in order to avoid contacting these participants again).

11.2.2 Minimizing the potential for coercion of patients to participate

Because members of the research team are involved in clinical care and research, there is the potential that some patients of the study team may be recruited. It will be made clear to all potential participants that participation is entirely optional and not a part of regular treatment. The bulk of the recruitment process will occur with the study coordinator, who does not treat patients in any of the clinical venues where recruitment will occur. Overall, the research team is experienced in clinical research and very mindful of the conflict between the dual roles of clinician and researcher. They firmly believe that the safety and desires of the patient take precedence over any research protocol, and work hard to assure their patients that research participation is not required for treatment. In the case where a patient of a study team member is recruited, the consent process and signature on the informed consent document will be obtained by the study coordinator.

11.3 Potential Risks and Minimization of Risks

11.3.1 Risk Associated with Screening and Assessments:

1) Risk of boredom, fatigue, or discomfort (likely, not serious). It is possible that participants will become fatigued, frustrated, or uncomfortable answering sensitive questions about their mental health history.

To minimize risk: Participants may request a break from the procedures and/or may decline to answer any questions, though they will be counseled that this could affect their eligibility to continue their participation. If a participant becomes so upset that he/she cannot continue, he/she may be withdrawn without penalty.

2) Loss of confidentiality around sensitive information (rare, not serious).

To minimize risk: Paper records with identifying personal information (consent form, payment records) are stored separately from research records in locked file cabinets behind locked doors, to which only authorized research personnel have access. All data will include a subject identifier number and no personally-identifiable information. A single tracking file contains links to the research records and participant codes. Computer records with identifying information are kept on secure, password protected servers. Staff are trained to scrupulously protect the confidentiality of sensitive information, and take care to limit the printing of documents with identifying information and to avoid unnecessary discussion of participant names. Screening forms for participants who do not qualify for the study will be destroyed, except for anonymous information unlinkable to the participants (such as age, gender, and education).

11.3.2 Risk Associated with Computerized Cognitive Training:

1) Fatigue or boredom while completing training exercises (likely, not serious). The cognitive training exercises used in this study are completed while participants are seated in front of a computer monitor or tablet screen. There are no known risks for these procedures, as they are entirely non-invasive and painless. It is possible that participants will become fatigued or frustrated while completing the training.

To minimize risk: Participants may take a break from the procedure or postpone completion to another day or time.

11.3.3 Risks Associated with tDCS.

Active tDCS may have no benefit. The general consensus is that tDCS is extremely safe. In a meta-analysis of over 200 tDCS studies conducted from 1998 to 2010, 56% of studies mentioned adverse events[12]. The events were generally minor, including itching, tingling, headache, burning sensation and discomfort limited to the scalp site where the tDCS electrodes were applied. To date, there have been no reports of seizures or other severe events induced by tDCS[12,13]. Importantly this is the case in both healthy volunteers and in different populations of patients, including patients with disorders where there might be an increased risk of seizures (e.g. Alzheimer's disease, recent stroke, epilepsy). For this study, an intensity not to exceed 2 mA will be used, for a duration of 20 minutes; little of this current actually reaches the brain since it must first pass through the scalp (skin, fat, etc), skull, and cerebrospinal fluid. Few, if any, side effects are reported with these parameters and those that are reported are mild in nature (e.g., tingling, itching, burning sensation; Nitsche & Paulus, 2011). Nevertheless, side effects of tDCS are possible. The most common side effects associated with tDCS based on the available scientific data are:

1) Sensations under the electrode: these sensations usually stop shortly after tDCS begins but can sometimes continue throughout and for a brief period after tDCS.
   - Mild tingling
   - Light itching
   - Slight burning sensation
   - Discomfort
2) Reported effects that occur only DURING tDCS:
   - Visual sensation during switching on and off the stimulation
3) Other effects that can occur both DURING and AFTER tDCS:
   - Fatigue
   - Skin redness
   - Headache
   - Changes in concentration, memory, or other cognitive abilities. This is partially what the proposed study will be testing.

Additionally, the following rare side effects have been described in previous studies that used tDCS:

1) Nausea
2) Nervousness
3) It is also possible that the electric current can cause a burn on the skin. This is unlikely because we are using a smaller dose than what is known to cause burns and because we use saline or gel to reduce electrical resistance that leads to burns.
4) A shock-like sensation at the initiation of tDCS was reported in one participant.
5) Changes in the activity of the prefrontal region (front of the head) have the potential to induce sudden changes in mood. Hypomania has been reported in a few patients receiving tDCS for bipolar disorder and depression.

To minimize risk: Clinically trained study staff will monitor participants closely for changes in mood or psychosis and/or any emergence of suicidal ideation throughout the duration of participation. In the event of significant symptomatic worsening (as detailed in *5.2.3 Stopping Rules*), the PI will be promptly notified, and plans will be formulated for additional emergency evaluation at the psychiatric emergency room (University of Michigan Psychiatric Emergency Services), if appropriate. Similarly, if the evaluation of a

participant uncovers suicidal plans or intentions, the same procedures for emergency evaluation will be followed.

Importantly, the majority of the above side effects have also been reported in association with sham (fake) tDCS, with similar rates. The table below comes from a recent review of tDCS safety and shows the percentage of studies reporting these common sensations[12]. These data suggest that other factors may cause these sensations, such as participant expectations or the pressure of head straps or caps.

Sensation	Real tDCS	Sham tDCS
Itching	39.3%	32.9%
Tingling	22.2%	18.3%
Headache	14.8%	16.2%
Burning	8.7%	10.0%
Discomfort	10.4%	13.4%

To minimize risk: The researchers will ensure that participants are fully informed of the risks during the informed consent process, and will adhere to best-practice standards for tDCS procedures.
Due to the investigational nature of the study, there may be risks, discomforts, or side effects that are not yet known.

For women of child-bearing potential: It is unknown if tDCS can pose a risk to fetuses or if it decreases milk production in women who are lactating.

To minimize risk: Participants are asked during their screening whether they are pregnant or are trying to become pregnant, or are currently lactating, and are not enrolled in the study if they are. Urine pregnancy screening can be made available to potential participants as requested. Sexually active women of child-bearing potential will be asked to use a reliable birth control method for the duration of this study.

11.4 Potential Benefits and Justification of Risks

Several randomized controlled trials have documented either benefits of tDCS for mental health conditions or no effect; we are not aware of any that have reported significant symptomatic worsening. tDCS is considered a safe procedure which poses no more than minimal risk. The purpose of this study is to investigate whether combined tDCS and computerized cognitive training can improve working memory skills; by taking part in this study, participants may demonstrate some improvement. It is also possible that participants will experience no change or a worsening of symptoms, which will be clearly described during informed consent.
This study will help clinical researchers develop and test effective interventions for people who experience serious mental health symptoms and may demonstrate neurocognitive impairment that can limit their everyday functioning. Ultimately, the goal of this research is to better understand the kinds of treatments that are feasible, meaningful, and helpful to participants with mental health conditions, in an effort to reduce disability and associated personal and societal costs.

12.0 Data Handling and Record Keeping

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Dark ink is required to ensure clarity of reproduced copies. When making changes or corrections, the original entry will be crossed with a single line, initialed, and dated. An electronic database will be used to store the coded data, and the key linking to identifiable participant information will be kept separate from the database with research data.

13.0 References

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