PROTOCOL TITLE:

Increased thalamocortical connectivity in tdcs-potentiated generalization of cognitive training

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VERSION NUMBER/DATE:

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
21	01/26/2023	● Added compensation for CT scan for MRI safety screening	No
20	12/14/2022	● Added optional CT scan for MRI safety screening ● Optional consent addendum form for CT scan added	Yes
19	4/8/2022	● Changed randomization groups in Cohort 2 to left active only	No
18	2/3/2022	● Added ResearchMatch as a recruitment source	No
17	11/9/2021	● Added burns as a side effect of tDCS to consent form and protocol ● Added exclusion iii: Five or more sessions of neuromodulation (such as tDCS) or cognitive training in the past 12 months ● Added mail ads as a source of recruitment ● Simplified some sections of the consent form, removing redundant or confusing language	Yes
16	10/25/2021	● Added outpatient Psychiatry clinic registry database as a method of recruitment	No
15	9/1/2020	● Changed wording throughout to accommodate remote study visit procedures	Yes
14	6/9/2020	● Added Section 5.7: Remote and Limited Study Operations ● Section 20.0: Added language for administering eConsent ● Added COPRR as a recruitment source	Yes
13	4/14/2020	● Added Suicide Risk Assessment to schedule of events tables ● Corrected definition of "cognitively impaired adults" in section 20.5 ● Added specifications regarding fluctuating capacity to consent in section 20.5	No
12	2/18/2020	● Fixed a typo in the compensation schedule	Yes
11	2/3/2020	● Changed compensation schedule, adding information about graded compensation and attendance bonus. ● Added recruitment poster, postcard, contact card for participants ● Updated study phone number and email ● Added QR codes for recruitment tools	Yes
10	12/27/2019	● Added Guild and Fairview sites and recruitment procedures for Study 2 (letters of support attached)	Yes

		● Added Release of Information for Guild patients to protocol and consent ● Added assessment audio/video recording to protocol and consent ● Added language describing payments for additional visits ● Added psychosis history questionnaire ● Removed Department of Psychology database from section 16 ● Added CMRR servers to section 16 ● Removed magnetic and optical media from sections 6 and 16 ● Modified the estimated IQ inclusion criteria range and uploaded updated IQ screen form	
9	9/30/2019	● Added compensation to CEDT	Yes
8	9/5/2019	● Changed exclusion criteria regarding psychiatric diagnoses to exclude only Serious and Persistent Mental Illness ● Clarified exclusion criteria regarding conditions with neurological sequelae to exclude concussion with hospital admission	No
7	7/25/2019	● Clarified that Cohort 2 participants may be recruited and screened using the online portal ● Explained visit timeline windows ● Replaced the PANSS with the BPRS and BNSS ● Clarified that UBACC will be used in both cohorts ● Explained that blinding code will be maintained by study statistician ● Changed randomization procedure description ● Clarified that some sensitive data is stored on secure servers (in addition to locked cabinets) ● Added consent language about costs of participation per updated guidelines	Yes
6	6/20/2019	● Clarified MRI contraindications and procedure for determining MRI safety clearance for subjects	No
5	5/23/2019	● Removed “6-panel” specification from drug screen language.	No

4	4/24/2019	● Added AUDIT, DUDIT and Smoking questionnaire ● Added Cognitive Effort Discounting Task ● Added TSRQ, BIS/BAS, NFC, and DPA self-reports ● Clarified IQ screen procedure ● Clarified use of online advertising ● Corrections to payment schedule and total ● Added graded compensation plan ● Added MCCB timepoints for cohort 1 (week 6 and week 12) ● Added medication review timepoint for cohort 1 (week 24) ● Clarified screening procedures for both cohorts ● Modified MRI N-back and DPX details ● Clarified that MINI does not assess for sleep disorders.	Yes
3	3/29/2019	● Increased age range to 18-60 years	No
2	3/7/2019	● Added language regarding DNA collection and analysis procedures, background rationale, as well as several consent form sections on DNA collection opt in/out and genetic confidentiality risks. ● Added second tDCS device. ● Modified task delivery platform description. Added notice of video and audio recording to consent form. ● Changed description of resting state MRI stimulus ● Removed language regarding not banking data for future use. Explained data banking plan. ● Changed prescreen IQ test and criteria	Yes
1	11/15/2018	Added language regarding NDA data sharing to protocol and consent form	Yes

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ABBREVIATIONS/DEFINITIONS

FC	functional connectivity
HC	healthy controls
MD	modeled dosage
tDCS	transcranial direct current stimulation
WM	working memory
SZ	schizophrenia or schizoaffective disorder
DNA	deoxyribonucleic acid
BDNF	brain-derived neurotrophic factor

STUDY SUMMARY

Study Title	Increased thalamocortical connectivity in tdcs-potentiated generalization of cognitive training
Study Design	Randomized Controlled Trial, Triple Blind
Primary Objective	To understand how tDCS with cognitive training affect thalamocortical circuitry in individuals with and without psychosis and to examine variability in response within both groups.
Secondary Objective(s)	To associate genotypes and epigenetic changes with variations in treatment response and outcome.
Research Intervention(s)/Investigational Agents	Transcranial direct current stimulation and magnetic resonance imaging
IND/IDE # (if applicable)	N/A
IND/IDE Holder	N/A
Investigational Drug Services # (if applicable)	N/A
Study Population	Healthy controls and individuals with schizophrenia
Local Sample Size (number of participants recruited locally)	180

1.0 Objectives

1.1 Purpose:

The overarching goals of this proposal are to deploy neuroimaging and cognitive testing to understand how tDCS with cognitive training affect thalamocortical circuitry in individuals with and without psychosis and to examine variability in response within both groups.

1.2 Secondary objective:

To associate genotypes and epigenetic changes with variations in treatment response and outcome.

2.0 Background

2.1 Significance of Research Question/Purpose:

The premise of the proposed work is that tDCS concurrent with multi-session working memory (WM) focused cognitive training facilitates durable increases in thalamo-prefrontal cortical (hereafter thalamocortical) functional connectivity (FC), and that this in turn enhances generalization to novel tasks. Due to its putative effects on plasticity and brain circuitry, tDCS is emerging as an important tool that may eventually be part of the next generation of psychiatric and neurological interventions(Andre Russowsky Brunoni et al., 2012). However, given the simple and non-focal nature of this intervention, significant questions about the mechanisms of action relevant to cognition remain unanswered (Bikson, Name, & Rahman, 2013; Flavio Fröhlich & Schmidt, 2013). Given that a 2 mA current from tDCS induces a low electrical field that causes subthreshold membrane polarization and does not carry any biological information, how can it potentiate improved performance on complex cognitive tasks or reduce diverse symptoms (Andre R. Brunoni et al., 2014; Kekic, Boysen, Campbell, & Schmidt, 2016; Trumbo et al., 2016)? Most critically for the current application, can understanding the neuroanatomy of tDCS-induced functional changes aid in optimizing tDCS for clinical applications?

2.2 Preliminary Data:

We have demonstrated that WM focused training increases left middle frontal gyrus (MFG) activity. This was first reported in a sample of n=9 experiment subjects with schizophrenia (compared to n=9 in the active control condition (Haut, Lim, & MacDonald, 2010)), and was recently replicated in n=15 patients (compared to n=12 in the active control (Ramsay, Nienow, Marggraf, & MacDonald, 2017)). We observed significantly greater increases in connectivity following WM training compared to the active control treatment in both right MFG ($\eta 2$=.35) and ACC ($\eta 2$=.29). These effects were driven by increased thalamocortical connectivity in the experimental group. Importantly, those who showed the greatest increases in thalamocortical connectivity also had the most general transfer on the MCCB in the experimental group (r=.55, p=.043, but not in controls.

As a proof-of-concept, we have also directly examined thalamo-prefrontal functional connectivity before and after tDCS intervention. To determine whether tDCS can directly affect thalamocortical connectivity, subjects were randomized to either active tDCS(n=6) or sham tDCS(n=5). Rest fMRI data was collected pre- and post-intervention. Intervention consisted of either cognitive training + active-tDCS or cognitive training + sham-TDCS twice a day (two 13 minute sessions per day, each 2mA / 25cm² = 0.08 current density; anode on left dorsolateral prefrontal cortex F3, cathode on right dorsolateral prefrontal cortex F4) for five consecutive days. Preliminary analyses examining FC between left thalamus and left dorsolateral prefrontal cortex showed that subjects assigned to active-tDCS (n=6) showed a within-group increase in FC (t=2.05, p=0.096) while subjects assigned to sham-tDCS (n=5) did not show a significant within-group FC change (t=1.103, p=0.332). Group x Time effects was eta-square $\eta 2$=0.353. These pilot data suggest tDCS can improve thalamocortical connectivity.

2.3 Existing Literature:

Task-dependent Nature of tDCS-enhanced Neuronal Plasticity. A growing consensus suggests tDCS acts as a modulator of ongoing synaptic activity to facilitate task-relevant plasticity. For example, anodal tDCS enhanced the induction of long-term potentiation (LTP) between concurrently active neurons in slice, but had no effect on inactive neurons (Kronberg, Bridi, Abel, Bikson, & Parra, n.d.). In living mice, a combination of training with stimulation enhanced both cortical LTP and motor learning in contrast to stimulation alone (Fritsch et al., 2010). This underscores the need for ongoing cognitive activity to realize the potential of tDCS.

TDCS-enhanced Cognitive Training. A major limitation of direct tDCS-enhancement of working memory (WM) appears to be that, upon meta-analysis, it leads to increased speed without increased accuracy on WM tasks (André Russowsky Brunoni & Vanderhasselt, 2014). Given this limitation, protocols interested in broader cognitive effects in healthy populations are increasingly using concurrent tDCS stimulation with training, such as WM training (e.g. 10 sessions, 2 mA left DLPFC,(Martin et al., 2013); 10 sessions, 1.5 mA left DLPFC, (Richmond, Wolk, Chein, & Olson, 2014); 7 sessions, 2 mA right and left DLPFC, (Au et al., 2016)). While tDCS- enhanced cognitive training, has only begun to be explored, there is evidence for greater training effects when training begins(Ramsay, Nienow, & MacDonald, 2016) and better generalization with right DLPFC stimulation (Au et al., 2016). However, as with single session tDCS-enhanced training (Trumbo et al., 2016), broad generalization of training with this number of sessions has shown limited results (none (Richmond et al., 2014) or a few tasks (Au et al., 2016; Martin et al., 2013; Martin, Liu, Alonzo, Green, & Loo, 2014)).

Thalamus and the Role of Thalamocortical Connectivity in Cognitive Generalization. We reject the hypothesis that tDCS-enhanced WM focused training works simply by enhancing local prefrontal cortical activity. Extensive animal research suggests that thalamocortical connectivity plays a key role in (i) modulating the attentional resources of the frontoparietal executive network(Zikopoulos & Barbas, 2007a), (ii) facilitating cognitive processes through connectivity throughout prefrontal cortex(Xiao, Zikopoulos, & Barbas, 2009), and that (iii) serving as a marker to investigate specific aspects of psychiatric illness(Zikopoulos & Barbas, 2007b). Our human studies suggest that WM focused training enhances DLPFC activity without evidence of generalization (Haut et al., 2010; Ramsay et al., 2016), which is consistent with local Hebbian mechanisms that support specialization (Marsolek, 2008). In contrast, the relationship between the thalamus and prefrontal-parietal circuitry has long been implicated in the general cognitive ability (or intelligence) literature (Fangmeier, Knauff, Ruff, & Sloutsky, 2006; Haier, Siegel, Crinella, & Buchsbaum, 1993; Osherson et al., 1998). While a review of thalamic architecture and its reciprocal connections to prefrontal cortex is beyond our scope, it bears mentioning that thalamus is the central hub for communication between sensory, association and motor regions, with thalamic nuclei projecting to cortical and subcortical areas throughout the brain and in a diffuse manner, terminating in various layers of cortex (Jones, 2009). Impairments in this hub function are linked to WM failures (Bor et al., 2011). Below we present pilot data suggesting the extent to which thalamocortical connectivity is enhanced in WM training predicts the extent to which generalization is observed. Importantly, tDCS enhances thalamocortical connectivity: anodal stimulation over left DLPFC or motor cortex (M1) temporarily increased thalamocortical cortex connectivity to their respective regions (Polanía, Paulus, & Nitsche, 2012)(Keeser et al., 2011)(Sours, Alon, Roys, & Gullapalli, 2014).

Cognitive and Thalamocortical Connectivity Impairments in Patients with Schizophrenia (SZ). Cognitive deficits are a prominent feature of schizophrenia and represent a large unmet treatment need with consequences for functioning (Barch & Sheffield, 2014; Green, 1996; Sheffield et al., 2014). Cognitive training is an intervention designed to improve cognition through repetitive practice with the goal of improving cognitive performance such as attention, memory, and problem solving (Cassetta & Goghari, 2016). While cognitive training is effective for improving cognitive abilities for some patients (Bosia et al., 2016), the process is time

and resource intensive (with as many as 48 1-hour sessions recommended) and many interventions show a lack of generalization (Dickinson et al., 2010). At the same time an increasingly compelling literature links thalamocortical FC impairments with schizophrenia, suggesting hyperconnectivity between thalamus and sensory regions (e.g. (Atluri, Steinbach, Lim, Kumar, & MacDonald, 2014)), and hypoconnectivity with prefrontal regions (e.g.(Anticevic et al., 2014)). The magnitude of hypoconnectivity even predicted conversion to psychosis among at-risk youth (Anticevic et al., 2015). Our findings, described below, that WM focused training improves thalamocortical connectivity in chronic patients with schizophrenia is therefore a hopeful advance in need of replication and extension (Ramsay et al., 2016).

Transcranial Direct Current Stimulation (tDCS) Studies in Schizophrenia. Various studies have reported promising effects of tDCS on medication-refractory clinical symptoms in schizophrenia (Brunelin et al., 2012; Andre R. Brunoni et al., 2014; F. Fröhlich et al., 2016; Goyal, Kataria, & Andrade, 2016; Shivakumar et al., 2013; Subramaniam et al., 2015), however the literature on tDCS's independent effect on cognitive deficits is quite mixed. Anodal stimulation showed small effects on attention (Smith et al., 2015), WM (Palm et al., 2016; Smith et al., 2015) but see also (Hoy, Arnold, Emonson, Daskalakis, & Fitzgerald, 2014) for a negative finding), memory (Smith et al., 2015) and general cognitive ability (Rassovsky et al., 2015; Smith et al., 2015). Marginal or negative effects were observed for processing speed (Palm et al., 2016; Smith et al., 2015). Cathodal stimulation showed comparably small results (Rassovsky et al., 2015). Our quantitative review of these findings failed to reject the null hypothesis in any domain of cognition for any modality of transcranial stimulation. Consistent with task-dependent nature of tDCS-enhanced neuronal plasticity, tDCS had its largest impact on SZ patients' cognitive impairments when repeatedly paired with concurrent WM cognitive training (Nienow, MacDonald, & Lim, 2016). This finding from our group is the clinical lead this study will replicate and examine.

Variance in Modeled Dosage. Physiological and behavioral responses to tDCS show high variability between participants. One possible source of variability in outcome is a variability in the induced electric field strength from participant to participant for identical electrode montages and applied intensities (Laakso, Tanaka, Koyama, De Santis, & Hirata, 2015; López-Alonso, Cheeran, Río-Rodríguez, & Fernández-Del-Olmo, 2014; Opitz et al., 2016; Wiethoff, Hamada, & Rothwell, 2014). Computational approaches have the potential to account for this variability using numerical methods to estimate the electric field distribution on an individual level. So far it has been untested whether numerical models can predict subject-specific variability in the response to tDCS. Recent intracranial field measurements (Huang et al., 2017; Opitz et al., 2016) and modelling studies (Laakso et al., 2015) have shown that applying a fixed intensity of 1mA can lead to large variations in the electric field strength in the brain across individuals. This variation in effective dose is a likely cause of the large interindividual variations in the physiological response to tDCS across participants (López-Alonso et al., 2014; Wiethoff et al., 2014). The possibility of computational models to account for this variability arising from interindividual anatomical variations (Opitz, Paulus, Will, Antunes, & Thielscher, 2015) has recently been recognized (Bestmann & Ward, 2017; Peterchev, 2017). Here we will directly test, whether individual realistic finite element method (FEM) models can account for observed variation in physiological and behavioral responses to tDCS.

The results from the proposed study on the effect of tDCS on thalamocortical connectivity in the context of WM focused training will provide critical information to inform future research work and clinical intervention studies.

Genetics and Treatment Response. Another source of treatment response variability could stem from differences between participants in baseline genetic profiles or epigenetic changes over the course of treatment.

Schizophrenia and associated spectrum disorders have a strong genetic component, with recent studies estimating nearly 80% heritability (Hilker et al., 2018). Genetic polymorphisms, particularly in genes relating to the dopaminergic and serotonergic systems, have been associated both with the development of the disorder (Harrison, 2015) as well as with varied response to pharmacologic treatments (Arranz & De Leon, 2007; McClay et al., 2011). Genetic polymorphisms, especially in genes important for neuroplasticity, may also mediate neuroplastic changes underlying the effects of tDCS (Chhabra et al., 2016), as has been demonstrated with gene BDNF (Antal et al., 2010; Fritsch et al., 2010). In light of these genetic influences on key tenants of our study--i.e. treatment response in schizophrenia and physiological effects of tDCS--we will collect genetic samples from participants to determine whether genetic or epigenetic variations may affect response to the cognitive training and tDCS intervention. This information may help inform the development of more individually-tailored treatment protocols in the future. As this is a secondary aim, participants will be given the choice in the consent form to opt in or out of the genetic sampling procedure.

Substance use as a moderator and outcome variable of tDCS. Individuals with schizophrenia and related disorders tend to exhibit high levels of substance use, particularly nicotine, alcohol, and cannabis (Margolese et al., 2004). Use of these substances has been demonstrated to be both an outcome and moderator variable in tDCS interventions. Smoking, in particular has been shown to attenuate the effects of a tDCS intervention on auditory hallucinations in schizophrenia (Brunelin et al., 2015), but also to restore impaired tDCS-related cortical plasticity in chronic smoking schizophrenia patients (Strube et al., 2015). In addition, tDCS interventions have proven capable of reducing various substance-related behaviors and craving (e.g. Boggio et al., 2008; Boggio et al., 2010; Falcone et al., 2016; Fregni et al., 2008; Klauss et al., 2014; but see Smith et al., 2015 for a negative finding). In light of the high prevalence of substance use in the schizophrenia population, and its potential as a significant moderator and outcome variable (albeit ancillary to our main hypotheses), we will track substance use throughout intervention.

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome:

SA1. Compare the effect of right active-tDCS, left active-tDCS and sham (hemisphere) in HC, the effect of left active-tDCS and sham in SZ, length of treatment and measured dosage on brain circuitry. In both HC and SZ, greater ipsilateral thalamocortical (prefrontal) FC increases relative to sham are driven by **H1.1** active tDCS in the ipsilateral hemisphere; **H1.2** a longer length of treatment; and **H1.3** higher modeled dosage.
SA2. Establish the effects of hemisphere, length of treatment and modeled dosage on generalization and durability. In both HC and SZ, greater generalization and durability are driven **H2.1** more by right tDCS compared to left tDCS or sham; **H2.2** by a longer length of treatment; and **H2.3** by higher modeled dosage.
SA3. Examine how changes in thalamocortical FC in both hemispheres affect generalization and durability. In both HC and SZ, greater thalamocortical FC drives **H3.1** greater generalization; and **H3.2** greater durability.
SA4. Examine relationships between genetic variants, epigenetic changes and treatment outcome (e.g. generalization, durability, functional connectivity).

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description:

This study will include 2 cohorts of participants (healthy controls and patients with schizophrenia) in order to evaluate how anodal tDCS with concurrent WM focused training affect thalamocortical connectivity, how this may differ from right vs. left (hemisphere) vs. sham stimulation, how the number of sessions (length of treatment) and modeled dose impacts proximal transfer and generalization, how they are affected by other psychologically and biologically relevant variables, and the durability of these cognitive changes after training.

For the proposed project, participants in cohorts 1 and 2 will undergo a similar protocol, consisting of WM training concurrent with tDCS. This training will consist of a target of 30 sessions of 45 minutes each in 11-12 weeks (target average density of 3 sessions/week), with a minimum of 24 sessions (and a minimum average density of 2/week). Due to limited reach to the schizophrenia population during the global pandemic, cohort 2 is expected to be a smaller sample size than originally anticipated. We will only be studying left hemisphere stimulation in cohort 2 subjects.

The tDCS will be performed with Neuroelectrics Starstim8 (Neuroelectrics Barcelona, Spain). This device has been approved for use in research without an investigational device exemption due to meeting criteria for non-significant risk. In addition, the device has built in safety mechanisms which allow for the immediate cessation of stimulation should the subject become uncomfortable or impedance levels too high.

The Starstim software supports the measurement of electrode impedance (Neuroelectrics, 2016). Before each training session, the impedance of the electrodes will be checked and verified to be ≤10 KOhm. During a training session, the impedance is measured every second and if found to be > 20 KOhm stimulation will be terminated for safety. The current and impedance will be recorded for every session (Ruffini, 2016) (implemented in Dec 2016, NIC v2.1).

We will take advantage of the ability of the Neuroelectrics StarStim8 (Neuroelectrics Barcelona, Spain) unit to programmatically control stimulation at multiple electrodes. During the intervention, subjects will wear a headband with electrodes at AF4 and AF3 (right and left DLPFC). Three different stimulation montages will be programmed: right, left and sham. Stimulation will consist of three periods: RampUp (30 sec), Constant (20 min), RampDown (30 sec). During the Ramp periods, 2 mA current will be delivered to both AF3 and AF4 with an ascending (RampUp) and descending ramp (RampDown) over 30 sec via two saline soaked electrode sponges (~ 25cm²; current density = 0.08 mA/cm²). In this way, all subjects experience the same sensation on both sides to blind them to condition. During the Constant period, current will be set based on the Condition: Right - 2mA AF4 anode-AF3 cathode; Left - 2mA applied to AF3 anode-AF4 cathode; Sham - current turned off. We will test and adjust this new blinding approach on healthy subjects prior to beginning the formal study. To assess subject perceptions of the intervention, we will ask what treatment they believe they received each session.

A second stimulation device will also be available for use in the study. The TaskFlow Transcranial Electrical Stimulation device (TaskFlow-TES) is a custom brain stimulation device developed in-house at the University of Minnesota. The TaskFlow-TES has been designed to provide the same functionality as the commercial device we are currently approved to use (Neuroelectrics StarStim8). Like the StarStim, the TaskFlow-TES is battery powered, communicates with the control computer via Bluetooth and monitors impedance and delivered current.

4.2 IND/IDE: N/A
4.3 Biosafety: N/A
4.4 Stem Cells: N/A

5.0 Procedures Involved

5.1 Study Design:

This is a triple-blind, randomized placebo-controlled clinical trial (with blinded subjects, experimenters and statisticians) with healthy controls (cohort 1) and schizophrenia patients (cohort 2). 90 HCs, after signing consent and determining eligibility will be enrolled and randomized to receive either (i) Active 2mA right (AF4

anode-AF3 cathode) or (ii) Active 2 mA left (AF3 anode-AF4 cathode), or (iii) Sham 0 mA tDCS during concurrent WM focused training for a total of 12 weeks. 90 SZ patients, after signing consent and determining eligibility will be enrolled and randomized to receive either (i) Active 2 mA left (AF3 anode-AF4 cathode), or (ii) Sham 0 mA tDCS during concurrent WM focused training for a total of 12 weeks. For the active stimulation, current will ramp-up for 30 seconds, remain at 2mA for 20 min and then ramp-down for 30 seconds at the end of the stimulation session. For sham stimulation, the electrodes will be placed at the same positions as for active stimulation (AF3 and AF4), but current will be turned off immediately after the initial 30 second ramp-up period. Thus, participants will feel the initial itching sensation associated with tDCS but will receive no active current for the rest of the stimulation period. This method of sham stimulation has been shown to be reliable(Gandiga, Hummel, & Cohen, 2006). To test the effects of dosage, we have scheduled a midtest and MRI scan after 6 weeks of training (approximately 15 sessions), and a posttest and scan at the completion of the protocol after 12 weeks (approximately 30 sessions). The assessment battery will be completed again at follow-up 12 weeks after the final training session.

5.2 Study Procedures:

Pre-Screening for Cohort 1 (healthy controls): Study staff or weblinks will direct interested individuals to a HIPAA compliant online portal with a thorough description of the requirements of the study. At this time, interested individuals will answer relevant screening questions, including tDCS or MRI contraindications. Volunteers will also complete items from a neuropsychological vocabulary test to estimate crystalized IQ. If the HC volunteer fulfills inclusion and exclusion criteria, they will be invited to participate and scheduled for the pretest assessment.

Pre-Screening for Cohort 2: Through a voice call or in-person meeting with study staff, or via the HIPAA-compliant online portal process described above for Cohort 1, interested individuals will be provided with a thorough description of the requirements of the study. Interested SZ volunteers will be asked screening questions about demographics, likely diagnosis, MRI eligibility and cognitive ability. Volunteers will also complete items from a neuropsychological vocabulary test to estimate crystalized IQ. Research staff will then inquire about the participant's transportation needs and offer assistance as needed to attend any in-person study appointments. If the SZ volunteer fulfills inclusion and exclusion criteria they will be invited to participate and scheduled for a pretest assessment.

Screening/Baseline Visit for Cohorts 1 and 2:

After the initial consent form has been signed, all participants will undergo the following assessments:

- The MINI – to rule out current Serious and Persistent Mental Illness (SPMI) and addictive disorders for Cohort 1, and to confirm diagnosis and rule out addictive disorders for Cohort 2.

Prior to randomization, eligible participants in both cohorts will be characterized at baseline and tracked across the study (see schedule of events tables) using cognitive tasks, clinical assessments, and neuroimaging. These include the following*:

- MATRICS Consensus Cognitive Battery Subtests (including Symbol-Coding, Category Fluency, Trailing Making Test, Spatial Span; Letter-Number Span; Hopkins Verbal Learning Test) (Cohort 1 and 2)
- UCSD-Performance Based Skills Assessment – Brief (UPSA-B) (Cohort 2 only)
- Brief Psychiatric Rating Scale (BPRS) (Cohort 2 only)
- Brief Negative Symptom Scale (BNSS) (Cohort 2 only)

* In the case that study assessment visits are conducted remotely, some of these measures (e.g. Spatial Span) will not be collected.

Assessment activities may be audio/video-recorded. These data will be reviewed by the study team in order to achieve reliability and consistency between different interviewers and to arrive at consensus ratings for assessment scores. Assessment audio/video data will be stored on a secured UMN Box server and will only be accessible by the study team. Participants will have the choice to opt out of assessment audio/video recording in the consent form.

In addition, all participants will provide a urine or saliva sample in order to complete a drug screen. Results will be recorded.

HC participants will be randomly assigned to one of the 3 groups: (i) Active 2mA right (AF4 anode-AFP3 cathode) or (ii) Active 2 mA left (AF3 anode-AFP4 cathode), or (iii) Sham 0 mA tDCS during concurrent WM focused training for a total of 12 weeks. SZ participants will be randomly assigned to one of the 2 groups: (i) Active 2 mA left (AF3 anode-AFP4 cathode), or (ii) Sham 0 mA tDCS during concurrent WM focused training for a total of 12 weeks. Neither participants nor experimenters will know group assignment. TDCS software programming will allow staff selection of the three hemisphere conditions (right, left, sham) corresponding to eight random letters (six to be distributed evenly among three conditions for HCs, two to be distributed evenly among two conditions for SZs) encoded to preserve the blind. Randomization will be facilitated and the blinding code will be maintained by the study statistician.

Neuroimaging Assessments/MRI (Baseline, Week 6, Week 12):
Participants who are able to do in-person study visits will complete MRI sessions using the 32 channel head coil on a 3T Siemens Prisma scanner (Siemens Erlangen, Germany) located in the Center for Magnetic Resonance Research (CMRR) at the University of Minnesota at baseline, midway through the intervention and post-intervention, at 12 weeks. MRIs will not be completed if there is any concern for participant safety. This includes safety concerns during the COVID-19 pandemic.

If the research team suspects that a participant may have metal in their body, the participant may have the option to undergo a low-dose, partial- or whole-body Computed Tomography (CT) scan prior to the MRI in order to ensure their safety and eligibility. The CT scan will take place at the CMRR at the University of Minnesota. Minnesota. A CMRR Safety Officer will determine the level of risk to the subject and whether they are approved for MRI scanning. If approved for scanning by professionals, all risks will be conveyed to the participant so they can decide whether they wish to complete the procedure. Any concerns from the review committee will be conveyed to the participant at that time. If a participant chooses to undergo a CT scan and is subsequently found to be ineligible for the MRI scan, they will still be compensated accordingly for their time.

The MRI scan (3T) takes about 75 to 80 minutes. MRI involves taking pictures of the participant's brain, from which the properties of certain brain tissues can be measured. While sometimes MRI scans are done for clinical purposes, the scans the participant will receive are being done for research purposes. Since these scans are not designed for clinical or medical reading, the participant's scans will not receive a clinical or medical interpretation. For the scan, the participant will be asked to lie down quietly on a bed, and the bed will slide into the scanner. Once the participant is inside the scanner, it will start to take the pictures. During the scan, the participant will simply lie quietly in the scanner with eyes closed while the scanner takes images of the participant's brain. The MRI scan will be performed at the University of Minnesota's Center for Magnetic Resonance Research.

<u>The MRI protocol:</u>

● Structural Imaging. High resolution whole brain anatomical T1 weighted (MPRAGE) and T2 weighted (SPACE) scans will be acquired using scan parameters matched to the HCP-lifespan protocol. Scan parameters are: T1: TE/TI/TR = 3.65/1100/2530 ms, flip angle = 7º, voxel size = 0.8 mm isotropic, scan time ≈ 7 min. T2: TE/TR = 564ms/3200 ms, variable flip angle, voxel size = 0.8 mm isotropic, scan time ≈ 6 min. The structural images will be processed through the Human Connectome Project (HCP) minimal preprocessing stream and are used in the data analysis for (a) image registration purposes and (b) structural volumetric measures for use as covariates in fMRI analysis.
● fMRI scanning. fMRI data will be collected using the HCP (http://www.humanconnectome.org/) multiband (MB) echo-planar sequence with parameters that closely match those used by the HCP-Lifespan project: echo time (TE) = 37 ms; repetition time (TR) = 800 ms; MB factor=8, flip angle = 52º; 72 oblique axial 2 mm thick slices; field of view (FOV) = 208 mm; 2 x 2 mm in-plane resolution (104 x 104 matrix size). The first 10 volumes will be discarded from data analysis to ensure that magnetization reached steady state. To avoid carryover task-related effects, rest will be collected before the other tasks (the order of which will be counterbalanced).
● Rest. Participants will keep their eyes open while they look directly at a small animated square which periodically rotates 45 degrees approximately every 60 to 180 seconds. Participants press a button whenever they perceive this change. This low-demand activity is used to objectively ensure that the participant is awake during the resting fMRI scan. The rest scan will have 900 volumes for a total scan time of 12 minutes.
● N-back Tasks. N-back tasks (Haut et al., 2010) will switch between 0-back and 2-back trials. A picture n-back will be done in scanner, and a word n-back will be performed the day of scan outside of the scanner. The word n-back includes one run, and the picture n-back includes two runs. Each run lasts approximately 6 minutes.
● DPX (Henderson et al., 2012; Poppe et al., 2016) task will be performed in several blocks. Each trial consists of a cue dot pattern followed by a probe dot pattern. One dot pattern was identified as a valid cue ("A" cue), and another as a valid probe ("X" probe). All other cues were invalid ("B" cues), and all other probes will be invalid ("Y" probes). Besides the valid "AX" target trials, 3 other possible combinations of cues and probes ("AY," "BX," and "BY") made up 3 distinct non-target trial types enabling the identification of a specific deficit in a subject's ability to maintain goal-relevant information throughout a trial. Timing will be jittered and each block of the DPX task will consist of 40 trials: 24 AX (6 0%), 6 AY (15%), 6 BX trials (15%), and 4 BY (10%). Each block will last approximately 6 minutes (Poppe et al., 2016).
● Field map Imaging. A pair of reverse phase encode spin echo EPI field map scans with the same prescription and voxel size as with the fMRI and with a total scan time ≈ 1 min. The field map images are used to correct the fMRI data for geometric distortions caused by magnetic field inhomogeneities as part of the HCP fMRI minimal preprocessing pipeline.

WM Training with tDCS (Weeks 1-12):
All participants will undergo WM training concurrent with tDCS. This training will consist of a target of 30 sessions of 45 minutes each in 12 weeks (target average density of 3 sessions/week), with a minimum of 24 sessions (and a minimum average density of 2/week). Individuals with fewer than 24 sessions will not be considered "complete". The training protocol is described below:

<u>TDCS Protocol</u>

Before each training session, the impedance of the electrodes will be checked and verified to be ≤10 KOhm. During a training session, the impedance is measured every second and if found to be > 20 KOhm stimulation

will be terminated for safety. The current and impedance will be recorded for every session. During the intervention, subjects will wear a headband with electrodes at AF4 and AF3 (right and left DLPFC)). Three different stimulation montages will be programmed: right, left and sham. Stimulation will consist of three periods: RampUp (30 sec), Constant (20 min), RampDown (30 sec). During the Ramp periods, 2 mA current will be delivered to both AF3 and AF4 with an ascending (RampUp) and descending ramp (RampDown) over 30 sec via two saline soaked electrode sponges (~ 25cm²; current density = 0.08 mA/cm²). In this way, all subjects experience the same sensation on both sides to blind them to condition. During the Constant period, current will be set based on the Condition: Right - 2mA AF4 anode-AF3 cathode; Left - 2mA applied to AF3 anode-AF4 cathode; Sham current turned off. We will test and adjust this new blinding approach on healthy subjects prior to beginning the formal study. To assess subject perceptions of the intervention, we will ask what treatment they believe they received each session.

WM Focused Cognitive Training Protocol.

WM focused training occurs on a computer and consists of a variety of exercises selected to i) place demands on the executive and storage functions of working memory ii) adapt to challenge the participant's current ability level, iii) provide ongoing feedback, and iv) present novel stimuli across verbal, visual and spatial modalities. Training tasks are developed in-house. Tasks for each subject are delivered from our AHC-IS server (cnc2.med.umn.edu). Responses of subjects and session audio and video are saved on our AHC-IS server for analysis of training performance and engagement. The aim of using multiple tasks that require WM functions is to engage thalamocortical connectivity in a number of different ways to promote generalization. The intervention will be provided by the experimenter in small groups of four or fewer participants (4:1 ratio of participants to experimenters) working under the supervision of Drs. MacDonald and Lim, in consultation with Co-I Dr. Nienow, following a protocol developed by Drs. MacDonald and Nienow. In this scheme, experimenters will monitor each participant's' training and customize the intervention to balance challenge and engagement. In addition, each week participants will perform 4-minute versions of a word and a spatial 3-back task that will remain the same across all weeks (but differ from the assessment versions) to allow us to track training improvements using a constant difficulty level.

Participant effort will be rated by experimenters at each session using the Work Behavior Inventory (Bryson, Bell, Lysaker, & Zito, 1997). Just before the end of each training session, subjects will complete a brief questionnaire that also asks about their perceived engagement in the training that day, as well as their mood, previous night's sleep, discomfort, and their perceived experimental condition. Finally, at the end of each session, the participant will select the final task from an array of fun games, which we have found promotes agency and improves attendance.

Genetic sampling procedures (Baseline and Week 12):
At the baseline and post-test visit, all participants will be given the option to provide a saliva sample for genetic analyses. A study staff member will provide the participant with written step-by-step instructions for the collection of a saliva sample using the Oragene DISCOVER saliva self-collection kit (DNA Genotek, Ottawa, ON, Canada, Catalog number OGR-500) and ask the participant to not eat, drink, smoke or chew gum for 30 minutes before giving a saliva sample. The total amount of saliva collected is approximately 2 milliliters (about half a teaspoon) and will take approximately 5 minutes to complete.

Nucleic Acid (DNA) Extraction:

Collected samples will be stored in the laboratory of Dr. Jeffrey R. Bishop at the University of Minnesota (516 Delaware Street S.E. Phillips-Wangensteen Building room B150 Minneapolis, MN 55455). Saliva samples will be processed for DNA using the prepIT extraction kit following the manufacturer's standard protocol (DNA Genotek, Ottawa, ON, Canada, catalog number PT-L2P-5). Extracted DNA will be quantified by the Quant-iT™ PicoGreen™ dsDNA Assay Kit (Invitrogen, Waltham, MA USA, Catalog number P7589) using the Synergy HTX mult-imode plate reader (BioTek Instruments, Winooski, VT, USA).

Genetic analyses:

DNA extracted from saliva specimens will be standardized to a working concentration of 10-25ng/l prior to analyses. Targeted gene variants will be genotyped using TaqMan SNP Genotyping assays and the Applied Biosystems 7500 Real Time PCR system (Applied Biosystems, Foster City, CA, USA), Restriction Fragment Length Polymorphism (RFLP) performed by fragment analysis on the 3730 Genetic Analyzer (Applied Biosystems), or multiplexed genotyping assays performed on the MassARRAY System (Agena Bioscience) at the University of Minnesota Genomics Core facility (UMGC). Genome-wide scale genotyping will be performed using microarray or sequencing techniques in consultation with the University of Minnesota Genomics Core (UMGC) For methylation detection studies, DNA extracted from saliva specimens will be bisulfite-converted using the EZ DNA Methylation Kit (Zymo Research, Irvine, CA, USA). Bisulfite-modified DNA will be PCR-amplified using primers designed to cover target gene regions for CpG site DNA methylation detection, and sequenced using the Illumina MiSeq system following a standardized protocol at the University of Minnesota Genomics Core facility (UMGC). Genome-wide methylation assessments will be performed using the Infinium MethylationEPIC BeadChip Kit (Illumina) (or comparable alternative) which interrogates over 850,000 methylation sites quantitatively across the genome at single-nucleotide resolution.

Motivation Questionnaires (optional):
At the baseline, week 6, week 12, and week 24 visits, participants in both cohorts will be given the option to complete a set of several questionnaires which assess motivation: the Treatment Self-Regulation Questionnaire (TSRQ) (based on Williams, Freedman, & Deci, 1998), the Defeatist Performance Attitude scale (DPA) (based on Weissman & Beck, 1978), the Need for Cognition Scale (NFC) (Cacioppo & Petty, 1982), and the Behavioral Avoidance/Inhibition Scale (BIS/BAS) (Carver & White, 1994). Individual differences in these traits may moderate performance and engagement with the study intervention. Participants who complete these questionnaires will be compensated an additional $10 for each visit they complete them (up to $40 additional compensation).

Cognitive Effort Discounting Task (CEDT; Baseline, Week 6, Week 12, Week 24):
Individual differences in motivation for cognitive effort may moderate performance in the cognitive training intervention (i.e., inadequate effort could impede performance). In order to assess motivation for cognitive effort in a performance-based manner, participants will be given a numbers task, adding up the sum of two displayed numbers and answering via keypress if the sum starts with T, S, F, or E. Participants will choose between receiving $5 (as a metric of points, not money paid out; hypothetical only except for random payout described below) for the harder version of this task or a value ranging from below $5 and above $0 for an easier version of this task. Harder tasks will range from 16 trials of the numbers task down to 4 trials. Easier tasks will range from 16> trials to >0 trials. Participants will be informed in the task instructions that they will be paid based on one of their choices in the task, selected at random. This amount will range between $0-5 based on the task parameters. The task will last approximately 10 minutes.

Assessment of Substance Use (Baseline, Week 6, Week 12, Week 24):
Alcohol, drug, and smoking behavior in both cohorts will be assessed at each timepoint using the Alcohol Use Disorder Identification Test (AUDIT; Saunders et al., 1993), Drug Use Disorders Identification Test (DUDIT; Berman et al., 2007) as well as several questions about smoking history and behaviors.

Schedule of Events for Healthy Controls

	Pre-screen	Screening/ Baseline Visit	Sessions 1-15 Weeks 1-6 (2-3 times/ weekly)	Mid-Test Week 6	Sessions 16-30 Weeks 7-12 (2-3 times/ weekly)	Post-test Week 12	Follow-up Week 24
Online screening questions	X						
IQ screen	X						
Randomization		X					
MATRICS Consensus Cognitive Battery Subtests		X		X		X	X
MINI[1]		X					
Suicide Risk Assessment		X		X		X	X
Drug Screen		X		X		X	X
Medication Review		X	X	X	X	X	X
Neuroimaging Assessment (MRI)[4]		X		X		X	

[1] The MINI will be administered prior to randomization.

WM Training with tDCS			X		X		
Genetic specimen collection (saliva)[2]		X				X	
CEDT		X		X		X	X
AUDIT, DUDIT, & Smoking questionnaire		X		X		X	X
TSRQ, BIS/BAS, NFC, DPA[33]		X		X		X	X

[2] Participants will indicate in consent form whether they choose to opt in or out of genetic sampling
[3] Optional questionnaires
[4] MRIs may not occur if in-person visits are a safety concern

Schedule of Events for SZ patients

	Pre-screen	Screening/ Baseline Visit	Sessions 1-15 Weeks 1-6 (2-3 times/ weekly)	Mid-Test Week 6	Sessions 16-30 Weeks 7-12 (2-3 times/ weekly)	Post-test Week 12	Follow-up Week 24
Screening Questions (phone)	X						
IQ screen	X						
Randomization		X					
MATRICS Consensus Cognitive Battery Subtests		X		X		X	X
UPSA-B		X		X		X	X
BPRS		X		X		X	X
BNSS		X		X		X	X
MINI[4]		X					
Suicide Risk Assessment		X		X		X	X
Psychosis history questionnaire		X					
Drug Screen		X		X		X	X
Medication Review		X	X	X	X	X	X
Neuroimaging Assessment (MRI)[7]		X		X		X	
WM Training with tDCS			X		X		
Genetic specimen collection (saliva)[45]		X				X	
CEDT		X		X		X	X
AUDIT, DUDIT, & Smoking questionnaire		X		X		X	X
TSRQ, BIS/BAS, NFC, DPA[6]		X		X		X	X

Visit windows: We will attempt to schedule study visits within approximately a one-week window (+/- one week) from the of the intended timeline. The time between a participant's screening/baseline visit and the start of their WM training (i.e., Session 1) may vary more flexibly, however. This timeframe is less critical than the timing of other visits, as it occurs before the participant receives the study intervention.

[4] The MINI will be administered prior to randomization.
[5] Participants will indicate in consent form whether they choose to opt in or out of genetic sampling
[6] Optional questionnaires
[7] MRIs may not occur if in-person visits are a safety concern

5.3 Study Duration:

- An individual will be enrolled in the study for approximately 24 weeks total to provide complete data.
- We anticipate requiring 4 years to enroll all subjects needed for this trial

5.4 Individually Identifiable Health Information:

We have submitted the University's Privacy Office online application for data privacy and security review. We will print and upload the application with this protocol.

5.5 Use of radiation: N/A

5.6 Use of Center for Magnetic Resonance Research:

Participants will complete three MRI sessions using the 32 channel head coil on a 3T Siemens Prisma scanner (Siemens, Erlangen, Germany) located in the Center for Magnetic Resonance Research (CMRR) at the University of Minnesota. This study will obtain CMRR PARS approval. Structural Imaging and fMRI scanning protocols included in Section 5.2.

5.7 Remote and Limited Study Operations

In the event of research constraints that reduce our capacity for face-to-face contact with subjects, or in cases where MR scanners are not available, we will still carry out as much of the original project as possible. This will be done by completing research procedures using remote data collection and task administration. We will provide subjects with the necessary software and hardware to support remote research procedures.

Remote study operations will proceed according to protocol, with the following differences:

- Study visits that would usually occur in-person will occur via a HIPAA-compliant video connection platform (such as Zoom) or via phone call.
- MRI procedures will not be necessary
- The MATRICS "Spatial Span" task will be dropped due to impracticality of remote administration
- tDCS cognitive training will be self-administered using remote contact with research staff. Training will proceed according to the current protocol, including regular communication with research staff.
- Consent, HIPAA authorization, and UBACC will be collected prior to the baseline visit (see section 20.0 for information on eConsent).
- After the consent, research staff will provide a package(s) to the participant containing the following:
    - 1 Linux appliance with a custom desktop application will be provided to the subject for conducting assessments and training. The custom desktop application running on the Linux appliance does not store any data locally. Collected data is stored on an HST supported server, cnc2.med.umn.edu. The appliance will have the capacity to provide computerized assessment, tDCS training, training tasks, and an integrated HIPAA-compliant video connection platform
    - 1 tDCS stimulation device and headband
    - Sufficient saline vials for the anticipated duration of remote training
    - Sufficient saliva drug screens for the anticipated duration of the study
    - 2 DNA saliva sample kits (if applicable)
    - 1 payment card to be activated and "charged" as appropriate according to the payment schedule
    - Any materials necessary for remote paper-and-pencil assessments (e.g. MATRICS test booklets, pencils, etc.)

    - Other materials as may be needed to complete the protocol, including return labels and packaging as needed for DNA saliva samples, laptop, and tDCS device
- Saliva drug screens and DNA sample kits will be done over Zoom so study staff can verify they are being done correctly by the participant
- All materials will be disinfected before and after shipping

6.0 Data and Specimen Banking

6.1 Storage and Access:

Data collected for this study will be maintained and stored in REDCap, Box and AHC-IS password protected servers.

Only research staff will have access to subject information. Records containing identifying information will be stored in a private research office in a locked file cabinet or on a secure server and will be accessible only by the principal investigator and study staff. The passwords for accessing this information will be available to only select staff that need access to the information to conduct their research duties.

All biological specimens for genetic analyses collected through this protocol will be stored in the laboratory of Dr. Jeffrey R. Bishop at the University of Minnesota (516 Delaware Street S.E. Phillips-Wangensteen Building room B150 Minneapolis, MN 55455). All specimens will be labeled and stored with a study specimen number, not with any personal or protected health information.

6.2 Data: List all of the data elements to be collected and banked for future use.

Data will be uploaded to the National Institute of Mental Health Data Archive (NDA) (see section 6.3 below).

Genetic data may be banked for future studies. Participants will choose on the consent form whether or not they wish for their specimens to be banked for future studies.

6.3 Release/Sharing:

The data collected may represent a unique resource for some investigators. We will make the de-identified data available to interested investigators who contact us for access to the data. As the proposed work is a clinical trial, the most appropriate database for our collected data appears to be clinicaltrials.gov. The investigator, co-investigator, and research staff will permit trial-related monitoring, audits, IRB/IEC(s) review and regulatory inspection(s) by providing direct access to source data/documentation.

Data will also be uploaded to the National Institute of Mental Health Data Archive (NDA), a repository run by the National Institute of Mental Health (NIMH) that allows researchers studying mental illness to collect and share information with each other. All personal information about research participants such as name, address, and phone number will be removed from these data and replaced with a code number before uploading to NDA. Research participants will be informed about NDA data sharing in the consent process and notified that they may choose to not participate in the study if they do not wish for their data to be shared with NDA.

7.0 Sharing of Results with Participants

7.1 Individual and group results, including results from genetic analyses, will not be directly shared with research participants. Participants will be informed that they can learn more about the outcome of this study upon completion at clinicaltrials.gov or on the investigators' personal laboratory research.

8.0 Study Population

8.1 Inclusion Criteria:

Cohort 1:
(i) ability to provide consent and comply with study procedures; (ii) age 18 to 60 years old; (iii) estimated IQ range within the specified range ($70 <= IQ_E <= 115$); (iv) no Serious and Persistent Mental Illness (SPMI) or addictive disorder diagnosis as measured by the MINI (Mini International Neuropsychiatric Interview; (Sheehan et al., 1998)), or sleep disorder; (v) ability to participate in three weekly 45' training sessions over 12 weeks and participate in four assessments.
Cohort 2:
(i) Ability to provide consent and comply with study procedures; (ii) age 18 to 60 years old; (iii) estimated IQ within the specified range ($70 <= IQ_E <= 115$); (iv) schizophrenia or schizoaffective disorder as assessed by the MINI (Mini International Neuropsychiatric Interview)(Sheehan et al., 1998); (v) not having a current addictive disorder as measured by MINI (Mini International Neuropsychiatric Interview), or a sleep disorder; and (vi) ability to participate in the intervention and assessments, as above; (vii) clinically stable and on stable medications for at least one month before start of study.

8.2 Exclusion Criteria:

Exclusion Criteria for Cohort 1 and 2:
(i) any medical condition or treatment with neurological sequelae (e.g. stroke, tumor, loss of consciousness >30 min, concussion involving hospital admission, HIV); (ii) contraindications for tDCS or MRI scanning (tDCS contraindication: history of seizures; MRI contraindications: The research team will utilize the CMRR Center's screening tools and adhere to the screening SOP during enrollment of all research participants in this protocol. The CMRR Center's screening tools and SOP are IRB approved under the CMRR Center Grant (HSC# 1406M51205) and information regarding screening procedures is publicly available on the CMRR website (CMRR Policies / Procedures); (iii) Five or more sessions of neuromodulation (such as tDCS) or cognitive training in the past 12 months

8.3 Screening:

Individuals interested in participating will be screened using a series of questions probing for inclusion and exclusion criteria.

Cohort 1: Study staff or weblinks will direct interested individuals to a HIPAA compliant online portal with a thorough description of the requirements of the study. At this time, interested individuals will answer relevant screening questions, including tDCS or MRI contraindications. If a volunteer appears eligible based on their answers to the online screening questions, study staff will call the volunteer on the phone to answer additional screening questions and to complete items from a neuropsychological vocabulary test. Alternatively, Cohort 1 volunteers can complete the entire screening process over the phone if needed. If the HC volunteer fulfills inclusion and exclusion criteria, they will be invited to participate and scheduled for the pretest assessment.

Cohort 2: Through a voice call or in-person meeting study staff will ask potential participants in Cohort 2 screening questions about demographics, likely diagnosis, MRI eligibility and cognitive ability. Alternatively, potential participants may complete elements of the prescreening process through the HIPAA-compliant online

portal described above. Volunteers will also complete items from a neuropsychological vocabulary test. Research staff will then inquire about the participant's transportation needs and offer assistance as needed to attend any in-person study appointments. If the SZ volunteer fulfills inclusion and exclusion criteria below, they will be invited to participate and scheduled for a pretest assessment.

Vocabulary test and IQ ranges: The purpose of the neuropsychological vocabulary test is to screen out individuals in both cohorts who are likely to fall outside the desired IQ range of $70 < IQ_E \leq 115$. Importantly, scores on the vocabulary test do not represent actual IQ *per se*, but will be used to efficiently estimate a range within which a volunteer's IQ is likely to fall.

- Cohort 1 (HC): because the mean IQ of the university community is approximately 115, we will use an estimated IQ (IQ_E) range $70 < IQ_E \leq 115$ for inclusion. This screening will substantially reduce the number of eligible participants, and is accounted for in our recruitment strategy.
- Cohort 2 (SZ): our goal is to study the portion of the SZ population that is most cognitively impaired and may therefore gain significantly from generalization of cognitive training, however we will also wish to rule-out cognitive disabilities. SZ mean performance on cognitive batteries is approximately 1 SD below the mean (85 IQ)(Dickinson, Ramsey, & Gold, 2007). We will use the estimated IQ range $70 < IQ_E \leq 115$ as appropriate for inclusion. We anticipate that this screening will not substantially reduce the number of eligible SZ participants as this is a large proportion of the population.

If potential participants in both cohorts meet the pre-screening criteria, they will be invited to participate and scheduled for a screening visit, where they will review and sign a consent prior to completing the screening assessment, which includes the MINI. The MINI will be administered in order to rule out current Serious and Persistent Mental Illness (SMPI) and addictive disorders for Cohort 1, and to confirm diagnosis and rule out current addictive disorders for Cohort 2.

9.0 Vulnerable Populations

9.1 Vulnerable Populations:

☐ Children
☐ Pregnant women/Fetuses/Neonates
☐ Prisoners
☒ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders
☐ Approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.
☐ Disadvantaged in the distribution of social goods and services such as income, housing, or healthcare
☐ Serious health condition for which there are no satisfactory standard treatments
☐ Fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior)
☐Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research
☐ Undervalued or disenfranchised social group
☐ Members of the military
☐ Non-English speakers
☐ Those unable to read (illiterate)

☐ Employees of the researcher
☐ Students of the researcher
☐ None of the above

9.2 Adults lacking capacity to consent and/or adults with diminished capacity (IQ 70-75) to consent:
One of the hallmark features of psychotic illnesses is diminished cognitive functioning. To date, there are relatively few treatments available for cognitive deficit. This study is a minimal risk trial and those with diminished cognitive functioning will not face greater risks by participating. In fact, we are matching the cognition level of the healthy comparison group in Cohort 1 (IQ 70-115) to that of the SZ group in Cohort 2. This is being done so that both groups will have the headroom to improve with the intervention. All participants must have capacity to provide informed consent at enrollment and throughout the study. Please refer to section 20.5 for the procedures to determine capacity to consent.

9.3 Additional Safeguards:
This research project is examining a potential treatment for impaired cognition in psychotic illnesses (Cohort 2); therefore it is necessary to include individuals with diminished cognitive functioning to evaluate the effectiveness of the proposed therapy. Both Cohort 1 and Cohort 2 will have the same range of cognition (IQ 70-115). All participants must have capacity to provide informed consent at enrollment and throughout the study. Please refer to section 20.5 for the procedures to determine capacity to consent.

10.0 Local Number of Participants

10.1 Local Number of Participants to be Consented:
We anticipate screening 300 healthy controls in order to enroll 90 participants in Cohort 1. We anticipate screening 130 SZ Patients in order to enroll 90 participants in Cohort 2.

11.0 Local Recruitment Methods

11.1 Recruitment Process:
Cohort 1: Healthy community (HC) sample:
Advertisements and postings announcing the study will be placed in University newspapers, organizational and departmental newsletters, online, and in public places. Study staff or weblinks will direct volunteers to a HIPAA-compliant online portal (REDCap) with a thorough description of the requirements of the study, such as the 3-day per week training for 12 weeks, and will allow them to answer relevant screening questions, such as tDCS or MRI contraindications. This mechanism is maintained through the College of Liberal Arts and has already been used in IRB approved studies.

Cohort 2 Patients with schizophrenia or schizoaffective disorder (SZ) sample:
SZ volunteers will be recruited directly from Guild Incorporated community mental health agency and Fairview Riverside Adult Day Treatment Center. Both organizations have provided letters of support, which are attached in ETHOS. SZ volunteers will also be recruited through referrals from other researchers at the University of Minnesota and from community and mental health agencies, paper and online postings, and in-person and telephone announcements made to support and advocacy groups. Through a call or in-person meeting study staff will provide a thorough description of the requirements of the study for SZ volunteers. Interested SZ volunteers will be asked screening questions about demographics, likely diagnosis, MRI eligibility and cognitive ability.

Patients from the Fairview Riverside Adult Day Treatment Center will primarily learn about our study through an IRB-approved flyer posted on a board (IRB approved) placed on a hallway wall at their treatment program.

They may also be told of the study by treatment program staff. If a patient is interested in participating in the study, they will be instructed to contact the study at a provided a study phone number or email address. Alternatively, we may provide a physical opt-in form (IRB approved) and instruct patients to return it with their name and signature to a locked box installed next to the flyer board. Only research staff have a key to access that locked box to ensure privacy, and will check the locked box regularly. Research staff will follow up with interested participants and set up a phone conversation or in-person meeting where the patient can learn more about the study and complete screening procedures.

All outpatients seen at the UMP Psychiatry Clinic are asked to complete a Consent to Contact for Research form to indicate if they are interested in being contacted for research opportunities. Study staff will request the contact information for those who have signed the consent form and meet basic inclusion criteria for the study, namely clinical diagnosis of a psychotic illness. Additionally, we have kept lists of previous participants or interested individuals who did not pass phone screens, who have consented to being contacted again in the future for further research opportunities. Individuals in both of these lists will be contacted by study staff, who will ask to describe the study to the individual on the phone and determine interest.
The Psychiatry Department has hired a Research Advocate who will be available to UMP clinic staff as a neutral party who can discuss research opportunities with patients. During a regularly scheduled clinic visit, the Research Advocate may briefly meet with the patient and ask them if they are interested in hearing about any research opportunities at the University of Minnesota. If the patient agrees, the Advocate will describe available studies which the patient may qualify for and if they are interested, provide contact information and recruitment materials to the patient. The Advocate may also ask if it would be okay to provide the patient's contact information to the study team or introduce them to study staff if they are available. The Advocate may also be responsible for asking patients to sign the consent form mentioned above which indicates if the patient may be contacted for research opportunities in the future.

Clinicians who see patients with psychotic illnesses within recruiting clinic locations may also discuss this study with their clients to see if they are interested in participating. If the client agrees, the provider may request that the client fill out a Consent to Contact for Research form, may ask to share their contact information with the study staff, or may provide them with IRB approved recruitment materials with contact information for the study.

The outpatient Psychiatry Clinic in the Department of Psychiatry & Behavioral Health at the University of Minnesota provides patients with the opportunity to indicate whether they are interested in being contacted to learn about research studies or whether they prefer to not be contacted. This is accomplished through provision of a secure electronic REDCap consent form. Access to the voluntary contact information is managed by the Department of Psychiatry & Behavioral Health and securely stored and accessed by the Institute for Health Informatics Data Warehouse (BPIC) at CTSI (UL1TR002494). The department's Research Recruitment Specialist partners with BPIC to request a registry database for specific, IRB approved studies. We are requesting permission to receive this contact information to recruit participants for study #STUDY00003506. We will only contact patients who have indicated an interest in hearing about research.

The Department of Psychiatry and Behavioral Sciences provides information about research opportunities for the public on a University of Minnesota webpage. Our study will be listed for public information and interest and include information about the study, including contact information, inclusion/exclusion criteria, IRB approval number, and purpose of study.

The Research Recruitment and Outreach Specialist (RROS), employee of the Department of Psychiatry, describes research opportunities to patients and provides study contact information to interested individuals. Potential participants may also provide confidential contact information to the RROS for the study coordinators. We will use advertisements on digital media platforms to reach our research population via demographic (geographically central to study site) and key words. Clicking the link will bring them to a link them to the informative REDCap database.

We will be using ResearchMatch as an additional source of recruitment. ResearchMatch.org is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University Medical Center. Potential volunteers will be contacted using the IRB-approved website recruitment language. Volunteers will then have the option of replying yes or no through a set of quick links available in the notification. If a volunteer chooses to respond in the affirmative, they will authorize ResearchMatch to release their contact information to me and we will be responsible for managing that information according to institutional guidelines.

We will use Quick Response (QR) codes on all printed and digital materials which will direct potential participants HIPAA compliant registry in REDCap.

We will utilize the Consortium of Psychosis Research Recruitment (COPRR) in the Department of Psychiatry & Behavioral Sciences. COPRR provides research participants with the opportunity to be added to a registry that contains their demographic and contact information, some assessment results, and study participation updates. The goal of COPRR is to reduce participant burden by centralizing recruitment and sharing assessment data that is collected in most studies. Data is stored in a secure REDCap database. Access to the database is controlled by the department's Research Recruitment & Outreach Specialist and is only granted after sufficient approval is confirmed. We will only use COPRR for its intended purposes and will follow guidelines from the COPRR PI for use of the database.

Email Communication with Potential Participants and Consented Participants: Potential participants may communicate with the study via email throughout the recruitment process. After signing the consent form and entering the study, however, if participants wish to continue communicating via email they must opt-in by signing a "Guidelines and Consent for Unsecured Email Correspondence for Research Participants." This form notifies participants of the confidentiality risks entailed in using unsecured emails, documents their consent to use this form of communication, and instructs them as to how to withdraw their consent at a later time should they choose to do so.

11.2 Identification of Potential Participants:

Healthy Controls: Potential participants will self-identify in response to advertisements and postings.
SZ cohort: Potential participants will self-identify in response to advertisements and postings, as well as through referrals from other researchers at the University of Minnesota. Potential participants will also be identified directly from Guild Incorporated community mental health agency and Fairview Riverside Adult Day Treatment Center (letters of support are attached in ETHOS) and from community and mental health agencies.

11.3 Recruitment Materials:

- Flyer (paper and online versions)
- Posters, contact cards, and rackcards
- Mail ads
- Newspaper ads

- Online portal (REDCap)
- Digital media ads
- QR codes linked to IRB approved contact portal
- Department of Psychiatry research opportunities website

11.4 Payment: subjects will be compensated according to the following schedule:
Baseline evaluation = $30
Follow-up at 6 weeks = $50
Follow-up at 12 weeks = $75
Follow-up at 24 weeks = $100
Intervention - 36 sessions (3 visits/week x 12 weeks) = up to $396 if all sessions are completed ($11 average per session)*
Attendance bonus = up to $60**
3 scans = $150
4 Motivation questionnaires (optional): $40
Cognitive Effort Discounting Task (optional): $0-5 per visit (x4 visits = maximum of $20)

Total possible compensation = $921

* Graded compensation for WM/tDCS sessions: Compensation for WM/tDCS sessions increases as a participant progress through the study. Sessions will be compensated at rates of $8, $10, $12, and $14 per visit. Payment tiers increase $2 every 9 completed sessions (if a participant attends 9 sessions at a given rate payment will increase to the next tier). If a participant misses a session, the payment does not go up until they have completed 9 sessions at a given rate.

** Attendance bonus: Additionally, if a participant completes 3 sessions in a week, they will receive a $5 attendance bonus for that week. Research staff will track participant attendance using a punch card and increase payment accordingly.

Participant travel and parking expenses: additional funds have been allocated in the budget to assist participants with travel and parking expenses on an as-needed basis. Participants will be informed in the consent form that these funds are available and to ask the research staff if they are interested in utilizing them.

Compensation for additional visits: Additional visits may be scheduled in order to recollect or finish collecting data (e.g. in the event that a standard study visit is disrupted by a technical issue such as equipment malfunction). In such cases, participants will be compensated for the additional time spent completing these study activities according to the following guidelines:

- For additional visits at involve assessment activities (activities normally completed at the Baseline or follow up visits at week 6, 12, or 24), participants will be compensated at a rate of $15/hr.
- For additional visits that involve training session activities (activities normally completed at the tDCS + cognitive training sessions), participants will be compensated for a full training session at the rate corresponding to their progress through the graded compensation plan mentioned above. A participant must still complete 3 successful sessions at a given rate in order to progress to the next compensation tier.
- If a participant terminates a visit early resulting in incomplete data, their compensation for that visit may be prorated according to the time spent during that visit.

- For other cases, compensation for additional visits or activities will be commensurate to the time and demands required of the participant for that visit/activity.
- An additional $10 will be provided as compensation for CT scans to confirm clear orbits as an MRI safety measure. CT scans will only be offered as needed for participants who have a history of metalworking and cannot be cleared to safely proceed with an MRI scan unless we have documentation of no metal fragments in the eyes. Only these participants will complete a separate consent form addendum which includes information about the additional $10 compensation.

12.0 Withdrawal of Participants

12.1 Withdrawal Circumstances:

- Participants will be able to discontinue study participation at any time.
- If at any time the study staff or clinical care team of the participant believes that it is unsafe for the participant to continue in the study, they will be removed.
- If the participant is not compliant with study procedures, they may be removed from the study at the discretion of the PI.
- If the participant is unable to tolerate the tDCS stimulation, technical adjustments will be made to improve tolerance. If these do not work, they will be withdrawn from the study.
- To protect vulnerable populations, if a patient that was deemed capable of providing consent goes through unforeseeable situations that may affect their capacity to consent, their capacity will be reassessed, and if not deemed capable, they will not be withdrawn from the study.

12.2 Withdrawal Procedures:

If participants are withdrawn from the study, the investigators will make a case-by-case determination as to whether they will collect any final assessment data after terminating the intervention. If it is unsafe for the participant to continue participating in the study, follow up data will not be collected. Any previously collected data will continue to be used in the data analysis.

12.3 Termination Procedures:

If at any point research staff is concerned about participant's welfare or behavior, they will notify participant that their participation in the study needs to terminate because of safety reasons. The participant will be paid for their time until their last active participation day. Data collected until the termination date will be used and considered incomplete.

13.0 Risks to Participants

13.1 Foreseeable Risks:

TDCS is considered to be a safe brain stimulation technique that rarely results in adverse events. The FDA has determined that it is a non significant risk device and consequently will not provide an IDE. There is currently no evidence of serious side-effects. Mild side-effects that typically resolve upon discontinuing tDCS include light itching or tingling under the electrode at the beginning of administration, skin redness, headache, fatigue, and nausea. A rare side effect of tDCS is a burn on the skin underneath the electrodes (less than 1 out of 500 sessions). The subject may choose to discontinue stimulation at any time during the session if experiencing excessive discomfort or side effects. Although seizures are not a known risk of tDCS intervention, anyone with a history or a risk for seizures will be excluded from the study. No other risks related to tDCS are anticipated.

To minimize risks regarding tDCS, study staff will be using standards of administration that have been shown as safe in numerous other studies using transcranial direct current stimulation. The length of administration of the current, size of electrode sponges used, and method of applying stimulation are the same as methods of administration that have been demonstrated as safe.

The other potential risks pertain to the maintenance of confidentiality. Participants will be probed for personal information during the interviewing process. As noted in the consent form, participants will be told that all diagnostic and other sensitive raw data will be kept in a locked file or secure server and available only to authorized investigators involved in this study. To minimize confidentiality risks, as noted in the consent form, all diagnostic and other sensitive raw data will be kept in a locked file or secure server and be available only to authorized investigators involved in this study. Genetic and epigenetic information will be for research purposes only and will not be included in participants' medical records. Genetic specimens and data will be labeled with the participant's study ID number and will not contain personally identifying information. Participants may opt-in to communication via email by signing a form, "Guidelines and Consent for Unsecured Email Correspondence for Research Participants", notifying them that unsecured emails pose a risk to confidentiality.

MRI risks. Individuals will complete a screening questionnaire for contraindications of MRI scanning. Any affirmative responses on the questionnaire will result in an interview regarding the possible contraindication. An attempt will be made to secure any records of the nature of the possible contraindication and this information will be reviewed by the PI and/or CMRR staff at the University of Minnesota. A determination will be made regarding the level of risk to the subject and whether they are approved for scanning. If approved for scanning by professionals, all risks to the subject will be conveyed to him or her so they can deliberate as to whether or not they want to complete the procedure. Any concerns from the review committee will be conveyed to the participant at that time. If the subject is not approved for scanning, the subject may not have the scan and will be excluded from that part of the study.

There are no known risks to humans due to the static magnetic field. Subjects, operators, and guests are carefully screened prior to entering the magnetic environment, and frequently reminded of the potential danger of introducing magnetic objects to the controlled area. Subjects are carefully screened and excluded from the study if they have any implanted devices. Subjects are always accompanied when near the magnet, and reminded to move slowly and carefully as they enter and leave the magnet.

The risk of tissue damage by energy emitted by the MRI device is controlled by compliance with FDA guidelines for commercial MRI devices. Safety devices are in place so that the magnet will cease to operate should any parameters begin to exceed their preset safety limits. The risk of peripheral nerve stimulation by dB/dt is limited by safety devices. The noise levels generated by each scan are monitored to ensure adherence to guidelines. In addition, subjects are provided with earplugs and secondary protection (foam covering or headphones) to increase comfort during the scan.

CT Risks. If a participant is suspected to have metal in their body and undergoes a CT scan, the CT scan involves exposure to ionizing radiation in the form of x-rays. Everyone receives a small amount of unavoidable radiation each year from space and from naturally occurring radioactive materials in the environment. The amount of radiation exposure received from a CT scan varies according to the size of the patient and the portion of the body that is scanned. The low dose CT scan performed for this study gives the body the equivalent of about 1 year or less of natural background radiation. The radiation discussed here does not include any exposure a participant might receive from their regular medical care. Generally, at such low radiation exposures, scientists disagree about the amount of risk and there may be no extra risk at all.

13.2 Reproduction Risks:
Since the MRI risks to fetuses are unknown, pregnant women are excluded from the study. The radiation from a CT scan may involve risks to an infant, embryo, fetus, or nursing infant which are not known at this time. Female subjects in child-bearing years are asked to confirm they are not pregnant.

13.3 Risks to Others: N/A

14.0 Potential Benefits to Participants

14.1 Potential Benefits: There is no guarantee of direct benefit to subjects.

15.0 Statistical Considerations

15.1 Data Analysis Plan:
Analyses to test SA1, whether ipsilateral thalamocortical (prefrontal) FC changes are affected by hemisphere, length of treatment or modeled dosage will be conducted separately for Studies 1 and 2. We will use FSL Randomise ("Randomise/UserGuide - FslWiki," n.d.) using non-parametric thresholding (5000 permutations, p-value 0.001) to avoid inflated false positive rates (Eklund, Nichols, & Knutsson, 2016), and threshold for significance using threshold free cluster enhancement (TFCE). Randomise design matrix files and contrast files ("GLM - FslWiki," n.d.) will model specific contrasts to compare the effect of right v. left active-tDCS or sham on thalamo-prefrontal FC. Main effects of hemisphere (right active-tDCS vs left active-tDCS and sham-tDCS H1.1), length of treatment (H1.2), and modeled dosage (H1.3) will be examined for each fMRI dataset (rest, N-Back, and DPX). Group x Time (pre-intervention, mid-intervention, post-intervention) interactions will also be examined for each fMRI dataset. In addition to motion correction and motion-related artifact removal, 24-parameter motion estimates will be included as regressors of noninterest (Power, Schlaggar, & Petersen, 2015). Rest. Rest will provide the most straightforward use of the regressor, which is to detect whether changes in thalamocortical connectivity exists. Since this test is in the absence of particular task demands any changes noted suggest trait-related functional connectivity changes. N-Back. Task-dependent connectivity associated with N-back task performance will be identified by modeling the block task design together with the thalamic regressor (similar to psychophysiological interaction (PPI) analysis (Friston et al., 1997)). Blocked fMRI analysis will allow us the best power to detect hemodynamic changes within brain networks related to working memory. The primary analysis for the N-Back tasks will consider the 2-back conditions alone. Subsequent analyses will examine the 2 > 0-back contrast to strengthen interpretation of any observed changes in task-dependent thalamocortical connectivity. DPX. Task-dependent connectivity associated with the DPX task demands will be identified by analyzing cue and probe events together with the thalamic regressor. Preliminary analysis for the DPX task will examine B-cue related connectivity alone, as this draws the most on proactive, WM-dependent, control. Subsequent analyses will strengthen interpretation by examining both B-cue > A-cue related connectivity, as well as connectivity changes associated with response-related, or reactive, control (during the AY condition). These analyses can all be completed before the blind is broken, with direction of any effects to be resolved after breaking the blind.

Analyses to test SA2, that generalization and durability are driven by right tDCS more than left tDCS or sham (H2.1), longer treatment length (H2.2) and higher modeled dosage (H2.3) will be conducted both between and within groups (for both Studies 1 and 2). The first step will establish the existence of between-group training effects using repeated-measures ANOVA's on the key performance outcome variables (d' scores for the word and picture N-backs, d'-context for the DPX, and the composite score for MCCB). We will also evaluate differences in self-rated engagement and experimenter-rated Work Behavior Inventory (Bryson et al., 1997), sleep patterns, age, baseline IQ, and these will be used as covariates of non-interest as appropriate.

To examine SA3, the relationship between thalamocortical FC change and generalization and durability, we will examine the nonparametric relationships between changes in thalamocortical connectivity and improvements on the trained task (word N-back d'), proximal transfer (picture N-back d'), and more distal generalization (DPX d', MCCB composite score) and durability (H3.1 and H3.2 respectively). If analysis of covariates suggest that there are important sources of within-group variance in learning (e.g. age, baseline IQ, etc.), then hierarchical regressions will be used on Fisher's transformed z-scores of thalamocortical connectivity. In addition, to determine whether thalamocortical FC changes predict stability in learning and generalization, task performance at 24 weeks will also be subjected to hierarchical regressions. The regression model will enter covariates on step 1, and thalamocortical connectivity on step 2. The statistician will be blind to condition until analyses are completed.

In all cases, these relationships will be tested separately for Cohort 1 and Cohort 2, as changes associated with improvement are likely to be different for groups with different mean levels of ability. Follow-up analyses will determine the extent to which these observed differences suggest actual differences between these populations. However, the current study is not designed to directly compare the populations.

15.2 Power Analysis:

75 completers in cohort 1 and cohort 2 will provide power of .80 to detect effects as small as $\eta 2=.03$ for key confirmatory analyses (tested at $\alpha = .05$) and $\eta 2=.05$ for other analyses (tested at $\alpha=.005$), with nearly as strong power for the analysis of the 24 week follow-up. The more conservative approach of intent-to-treat analysis (n=90) will also be conducted for Cohort 2, for which the study will be sensitive to $\eta 2=.027$ (tested at $\alpha = .05$) and $\eta 2=.042$ (tested at $\alpha = .005$). These effect sizes are much smaller than the group x time effect for generalization as measured by the MCCB in our pilot tDCS data ($\eta 2=.08$), suggesting the proposed study is well-powered. While power analyses for neuroimaging studies are challenging due to the interactions of voxelwise-thresholds, brain-wise error correction and spatial smoothness, the proposed studies will be well-powered to detect group x time voxel differences as small as $\eta 2=0.07$ (tested at $\alpha = .001$), and in any case the samples are twice the size of our previous, successfully replicated, neuroimaging studies of brain change following cognitive remediation. Within-group responder analyses conducted for completers (n=25 per cell) will have power of .80 to detect correlations $r \geq .34$, a lower magnitude that we already observed (r=.55).

15.3 Statistical Analysis:

See section 16.1

15.4 Data Integrity:

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. To enhance scientific rigor, avoid bias and enhance reproducibility, our triple-blind randomized design will use a stratified permuted block randomization procedure (Matts & Lachin, 1988) to roughly equate age and baseline WM performance across groups with a block size of 6. Neither participants nor experimenters will know group assignment. TDCS software programming will allow staff to randomly select one of the three hemisphere conditions (right, left, sham) corresponding to eight letters (six to be distributed evenly among three conditions for HCs, two to be distributed evenly among two conditions for SZs) encoded to preserve the blind. Randomization will be facilitated and the blinding code will be maintained by the study statistician.

16.0 Confidentiality

16.1 Data Security:

Only research staff will have access to subject information. All records, including those containing identifying information, will be stored in one of the following manners:

- in a private research office in a locked file cabinet;
- in the University of Minnesota supported REDCap database;
- University of Minnesota secured BOX files
- AHC-IS maintained server
- CMRR servers (imaging data)
- secured laboratory (biological samples)

Passwords will be required to access study data stored electronically or in a database. Study data will be available only to select staff that need access to the information to conduct their research duties and to computer system administrators via password.

To minimize the volume of documents containing identifying information, all study documents or data will contain a unique participant ID that will be used when possible.
No copy of the consent form or other research study information will be placed in the participant's medical, employment, or educational records.

17.0 Provisions to Monitor the Data to Ensure the Safety of Participants

17.1 Data Integrity Monitoring.

The PI will be responsible for data accuracy and quality assurance (e.g., data collection, entry, transmission, and analysis), and study management (e.g., enrollment, integrity of study procedures).
The study will be monitored by CTSI in accordance with its institutionally approved monitoring plan.

17.2 Data Safety Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

18.0 Provisions to Protect the Privacy Interests of Participants

18.1 Protecting Privacy:

The study consent form will describe in detail any intrusive, uncomfortable, or unfamiliar questions, procedures, or interactions with researchers or study personnel that the participant will be asked to complete. Furthermore, the study consent form will communicate that it is the participant's right to opt-out of any study procedures or the study as a whole or withdraw from the study at any time and this information will be reiterated and revisited periodically throughout the study in advance of intrusive, uncomfortable, or unfamiliar questions procedures or interactions. Participants will not be compelled or pressured to provide information or specimens or study data that they do not wish to provide.

18.2 Access to Participants:

The research team will not access any medical records from participants.

19.0 Compensation for Research-Related Injury

19.1 Compensation for Research-Related Injury:

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to the participant or his/her insurance company.

19.2 Contract Language: N/A

20.0 Consent Process

20.1 Consent Process (when consent will be obtained):

Prior to the baseline visit, all subjects participating in this study will be required to provide informed consent and HIPAA authorization using an eConsent (electronic consent) form. Only the staff obtaining consent, the subject, and any family members invited by the subject will be present. The research coordinator or other trained research staff will explain the study to the participants. After explaining the study, the participants will be allowed as much time as needed to review the consent document and ask any questions that might arise before making the decision to participate. If necessary, participants can delay participation and return to sign the consent form at a later time. Subjects will be allowed to review the consent form in private for as long as they need. Subjects will be encouraged to ask any and all questions prior to providing consent. Study personnel obtaining consent will emphasize first and foremost that the study is voluntary and will not influence that subject's clinical care or their relationship to the University of Minnesota. No participant will be under legal commitment at the time of their consent or during their participation in the study, and surrogate consent will not be allowed.

The IRB-approved eConsent form will be administered as a REDCap survey. We will follow SOPs from the Psychiatry department on carrying out remote eConsent.

Participants will be offered a physical and/or electronic copy of the consent form and HIPAA authorization to read through during the consent discussion. If the participant agrees to participate, they will sign the consent form and HIPAA authorization.

Participants recruited from Guild Incorporated will be asked to sign an optional Release of Information form provided by Guild Incorporated (attached in ETHOS) as well as to initial an additional, optional section of the informed consent form (provided in ETHOS) that grant permission for the study team to confirm eligibility criteria with the participant's case manager at Guild Incorporated.

Consent to continue in the study will be addressed before each scheduled visit. The participant will be reminded that their participation in this study is completely voluntary and they do not have to continue unless they want to do so. In addition, if at any point during the study the staff has reason to suspect that the individual's capacity to provide consent has diminished (e.g., the participant has increased psychotic symptoms), the study staff may choose to re-administer the UBACC to confirm that the participant has capacity to provide ongoing consent. If the participant does not show capacity to consent, the PI will review their case and determine whether it would be best to withdraw them from the study completely or pause their participation until capacity to consent returns.

20.2 Waiver or Alteration of Consent Process (when consent will not be obtained): N/A

20.3 Non-English Speaking Participants: We will not enroll participants who do not speak English

20.4 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): We will not enroll participants under 18 years of age.

20.5 Cognitively Impaired Adults (IQ 70-75), or adults with fluctuating or diminished capacity to consent:

- Cohort 1 subjects are healthy community volunteers.
- Cohort 2 will be subjects who have a psychosis disorder but are clinically stable.
- We will use the UBACC to assess capacity to consent for both cohorts.
- The UBACC will be re-administered at any point if we have reason to believe that there has been a change in capacity to consent due to any of the following:
    - Confusion or disorientation (i.e. not knowing the current time or date)
    - Inability to complete training and tasks that had been done previously

Inability to understand or follow directions

20.6 Adults Unable to Consent: We will not enroll adults unable to consent.

21.0 Setting

21.1 Research Sites:

- Research visits will take place in the Department of Psychology, CTSI Delaware Clinical Research Unit, 717 Delaware Ave. building, Psychiatry Dept Ambulatory Research Center, the Center for Magnetic Resonance Research (CMRR) and Guild Incorporated in St. Paul.
- Biological samples for genetic analyses will be stored and processed at the laboratory of Dr. Jeffrey R. Bishop at the University of Minnesota (516 Delaware Street S.E. Phillips-Wangensteen Building room B150 Minneapolis, MN 55455).

21.2 International Research: N/A

22.0 Multi-Site Research

N/A

23.0 Resources Available

23.1 Resources Available:

- We propose to enroll 180 participants (90 HC and 90 SZ). We have conducted longitudinal studies with similar recruitment numbers without issue. We will use recruitment approaches available through our University Clinics, Clinical Translational Science Institute, community partners, advertisements (online and print), flyers and university community resources. We will monitor our recruitment progress and expand outreach if the recruitment goals are not meeting project targets.
- Our study staff are all equipped with desktop computers to conduct data entry and other study related tasks. All desktop computers are connected to dedicated secure Ethernet cords connected to the UMN secure networks and require passwords to log on. No identifying information will be stored on desktop computers. Additionally, we have two laptops for tDCS administration which will also be connected to the UMN secure networks. We have the necessary facilities to print subject binders. We have a StarStim tDCS system.

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