# PROTOCOL TITLE:

Transcranial Direct Current Stimulation and Cognitive Remediation Therapy for Psychosis

# PRINCIPAL INVESTIGATOR or FACULTY ADVISOR:

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# VERSION NUMBER/DATE:

Version 17.0 Date 27MAY2022

# REVISION HISTORY

| Revision # | Version Date | Summary of Changes | Consent Change? |
|---|---|---|---|
| 2.0 | 7FEB2018 | -Exchange WAIS assessment for WTAR<br>-Updated EEG device, protocol description<br>-Remove midpoint PANSS assessment<br>-Change 3 month follow up appointment to a 1 month follow up appointment<br>-Update Consent and HIPAA forms<br>-Update Consent process: consents will now be digital and captured on an iPad<br>-Update research storage process: all research forms (PANSS, MINI) will be scanned into the secure Box file and then shredded | Yes |
| 3.0 | 20APR2018 | - Change accepted diagnoses to Schizophrenia and Schizoaffective<br>- Change MINI to abbreviated version consisting of mood, mania, and psychosis modules<br>- Add PositScience FaceMorph assessment, to baseline, post, and 1-month follow-up<br>- Add Social Functioning Scale and Quality of Life Scale to baseline and 1-month visits<br>- Added VRFCAT assessment | Yes |

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| | | - Remove Barratt Impulsivity Scales<br>- Break baseline assessments into two visits<br>- Updated compensation to $255<br>- Adding new recruitment flyer and contact card | |
| 4.0 | 24JUL2018 | - Add questionnaire asking about participant blinding<br>- Add a tolerability questionnaire<br>- Add a handedness questionnaire<br>- Allow WTAR/ Edinburgh Handedness Scale to be administered during consent or baseline assessments | Yes |
| 5.0 | 07AUG2018 | - Removed language allowing pregnant women | No |
| 6.0 | 07 DEC 2018 | -Changed appointment and payment schedules<br>-Added MMN and ASSR assessments to EEG visits<br>-Updated inclusion and exclusion criteria<br>-Added risks of communicating via email<br>-Updated recruitment poster and cards<br>-Updated phone screen<br>-Updated consent form<br>-Cleaned up language in protocol, consent form, and phone screen | Yes |
| 6.1 | 07 JAN 2019 | -Removed sentence from Potential Benefits section, per IRB request<br>-Clarified how emails will be de-identified<br>-Clarified data collection and storage procedures, including a data flow diagram | |
| 7.0 | 18 FEB 2019 | -Specified passing score for UBACC<br>-Added compensation for parking expenses<br>-Added DPX, Web-Surf, and PSS tasks/measures | Yes |

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| | | -Added ability to use diagnostic assessments from other studies<br>-Updated Data Flow Diagram<br>-Clarified means of completion for assessments on schedule of events<br>-Added ability to text participants from a University-owned cell phone<br>-Added text authorization form<br>-Added un-encrypted email authorization form<br>-Updated payment schedule<br>-Updated data storage procedures<br>-Updated recruitment materials | |
| 7.1 | 02 APR 2019 | -Specified a 12-month outer limit for recency of diagnostic data obtained from other studies<br>-Specified collaborating labs<br>-Clarified that text and email communication are optional elements on the consent form<br>-Updated website study description | |
| 8.0 | 10 MAY 2019 | -Changed Ian Ramsay to PI (reflected on relevant study documents)<br>-Updated total enrollment goal in protocol and consent<br>-Updated storage procedures for EEG data<br>-Removed sentence in protocol about “date of birth” storage that contradicted another sentence in the protocol<br>-Added language to the consent about excluding people who are pregnant or possibly pregnant<br>-Edited language on website study description to be easier to understand by a non-academic audience<br>-Updated withdrawal circumstances for hospitalizations<br>-Updated exclusion criteria | Yes |
| 8.1 | 19 JUN 2019 | -Corrected total enrollment from 30 to 85 | Yes |

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| | | -Clarified reasoning behind exclusion of pregnant women in consent form | |
| 9.0 | 20 AUG 2019 | -Removed Web Surf task<br>-Added fMRI including structural T1/T2, Rest, N-back Task<br>-Added risks of EEG | Yes |
| 10.0 | 18 MAR 2020 | -Updated withdrawal procedures for on-study hospitalizations<br>-Updated devices that can be used for some assessments<br>-Updated times of appointments<br>-Added ability to recruit and use data from the COPRR registry<br>-Updated consent form to combined Consent/HIPAA<br>-Updated phone screen<br>-Added MSI as a location to analyze imaging data<br>-Removed FaceMorph from all timepoints | Yes |
| 11.0 | 22 JUL 2020 | -COVID-19 adaptations<br>-Allow for some remote research activities through Zoom or phone call, including consent procedures<br>-Allow some research activities to be skipped if risk of COVID-19 transmission becomes too great<br>-Allow participants to complete 2 tDCS/CRT sessions per visit to reduce total number of visits, if desired<br>-Added information about crisis situations<br>-Require mask use by participants during most in-person procedures<br>-Added COVID-19 Stress Screener Survey<br>-Added COVID-19 Screening Tool<br>-Added risk of COVID-19 infection and information about mitigation efforts that will be taken by staff<br>-Update and correction to UBACC | Yes |
| 12.0 | 14 OCT 2020 | -Added third arm (tACS) | Yes |

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| | | -Increased target sample to 105 individuals<br>-Added Sound-Induced Flash Illusion<br>-Updated electrode sponge size<br>-Added participant-facing Cognitive Training Instructions document<br>-Updated recruitment and consent materials to account for third arm | |
| 13.0 | 02 FEB 2021 | -Corrected Sound-Induced Flash Illusion Task to a Flash-Illusion Task<br>-Softened language regarding long term risks of tDCS and tACS<br>-Clarified protocol language about completing BAC remotely | Yes |
| 14.0 | 07 APR 2021 | -Updated sunrise plan to allow volunteers to safely return to in-person work<br>-Removed optional fMRI from all time points (and updated all relevant recruitment materials)<br>-Added Binocular Surround Suppression task to Baseline and Post-Training time points<br>-Updated COVID-19 screening to align with IRB guidance and new MN DOH guidelines | Yes |
| 15.0 | 25 JUN 2021 | - Added recruitment details with regard to recruiting through community mental health services and agencies<br>- Updated study staff contact information on consent form and recruitment materials<br>- Added ability to reimburse participants for costs related to transportation to study visits | Yes |
| 16.0 | 6 AUG 2021 | -Update payment amount for stimulation sessions on protocol, consent, and recruitment materials<br>-Removed Flash Illusion task from protocol<br>-Updated COVID-19 Screening form | Yes |

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| 17.0 | 27 MAY 2022 | -Added language stating that the study team would use remote/pencil/paper version of the BAC app. | |

## Table of Contents

# ABBREVIATIONS/DEFINITIONS

- ASSR: Auditory Steady State Response
- BAA: Business Associates Agreement
- BACS: Brief Assessment of Cognition in Schizophrenia (BACS)
- COPRR: Consortium of Psychosis Research Recruitment
- C-SSRS: Columbia Suicide Severity Rating Scale
- CRT: Cognitive Remediation Therapy
- DPX: Dot Pattern Expectancy Task
- DUA: Data Use Agreement
- EEG: Electroencephaologram
- fMRI: Functional magnetic resonance imaging
- NOS: Not otherwise specified
- PANSS: Positive and Negative Syndrome Scale
- MMN: Mismatch Negativity
- PSS: Perceived Stress Scale
- QoLS: Quality of Life Scale
- SFS: Social Functioning Scale
- SZ: Schizophrenia
- tCS: Transcranial Current Stimulation
- TCT: Targeted Cognitive Training
- tACS: Transcranial Alternating Current Stimulation
- tDCS: Transcranial Direct Current Stimulation
- VRFCAT :Virtual Reality into the Assessment of Functioning in Clinical Trials
- WTAR: Wechsler Test of Adult Reading

# STUDY SUMMARY

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|---|---|
| **Study Title** | Transcranial Direct Current Stimulation and Cognitive Remediation Therapy for Psychosis |
| **Study Design** | Randomized Controlled Trial, Double Blind |
| **Primary Objective** | To investigate whether tDCS enhances the effect of cognitive remediation therapy on cognition and functional outcome by comparing active vs. sham testing on the BACS |
| **Secondary Objective(s)** | To determine if tDCS and CRT will enhance functional brain activation measured by EEG over sham tDCS and CRT |
| **Research Intervention(s)/Investigational Agents** | -Transcranial Direct Current Stimulation compared to sham stimulation<br>-Cognitive remediation therapy |
| **IND/IDE # (if applicable)** | N/A |
| **Investigational Drug Services # (if applicable)** | N/A |
| **Study Population** | Outpatients diagnosed with Schizophrenia or Schizoaffective disorder |
| **Sample Size (number of participants)** | **105** |
| **Study Duration for Individual Participants** | Approximately 2 months |

# 1.0 Objectives

*1.1* Purpose: The proposed pilot study is a randomized controlled study to assess the effectiveness of transcranial Direct Current Stimulation (tDCS) to enhance cognitive remediation therapy (CRT) in patients with schizophrenia and schizoaffective disorder. We will determine whether any observed changes in symptoms and cognition are greater in participants who receive concurrent tDCS and cognitive remediation therapy as compared to individuals who receive sham stimulation. Additionally, we will determine whether there are functional changes in participants who received active vs. sham tDCS by comparing EEG data from both groups.

# 2.0 Background

*2.1* Significance of Research Question/Purpose:

**Cognitive dysfunction is associated with disrupted prefrontal gamma in schizophrenia:** Cognition in schizophrenia (SZ) is characterized by broad and pervasive deficits observed across most neurocognitive domains[1], and is associated with poor functional outcomes[2]. Therefore, cognition is a treatment priority for individuals with SZ and related disorders, but the specific neural mechanisms that underlie this aspect of SZ pathology are not fully understood. Accumulating research has pointed to disruptions in prefrontal gamma oscillatory power that underlie a range of cognitive deficits in SZ, including early sensory processes[3] and higher-order cognitive control operations[4–6]. Studies in both animals and healthy adults demonstrate that cortical circuit performance can be enhanced by neural synchronization in cortical networks driven by gamma oscillations[7–10]. This suggests that disrupted gamma may be a core pathophysiological mechanism underlying cognitive deficits in SZ, and therefore a crucial treatment target for improving outcomes.

Targeted cognitive training (TCT) is a computerized behavioral intervention that seeks to mechanistically target the sensory processing and integration disruptions that underlie some of the hallmark cognitive deficits observed in SZ[11]. This treatment adaptively exercises basic auditory, visual, and working memory processes to harness plasticity in temporal[12], prefrontal[13], and thalamocortical circuitry[14]. Previous findings indicate that 40-50 hours of TCT yields improvements in global cognition in patients with both early[15] and chronic SZ[16]. Cognitive improvements have also been observed in as few as 20-40 hours of the intervention[17,18]. TCT has also been shown to influence functional, structural, and electrophysiological plasticity. 40 hours of training was associated with increased activation in prefrontal brain areas associated with working memory[19] and social cognition[20], as well as morphological changes observed in the thalamus that corresponded to

improvements in overall cognition (Ramsay et al. In Press). TCT has also been demonstrated to normalize physiologically measured sensory processing and attention (i.e. sensory gating) in SZ [18]. Notably, in response to training, prefrontal high gamma oscillatory power increased and corresponded to cognitive improvements[21,22].

More efficient cognitive training strategies are necessary to develop a truly viable clinical treatment: TCT is a promising treatment to target cognitive deficits via disruptions in oscillatory gamma, but remains limited due to the heavy participant burden. Despite efforts to embed motivational and rewarding stimuli into TCT, treatment remains a major challenge. In previous TCT trials, ~36% of participants dropped out of the active training condition[23] (compared to 24% in the control condition), and those who did complete the study only achieved an average of 32.93 hours (out of 40 assigned) of training over the course of 2 months[15]. These participants self-reported "slight" enjoyment in response to TCT, suggesting that in spite of the cognitive benefits, individuals may have difficulty engaging for 8-10 weeks in such a treatment. Additionally, null findings have been shown in response to TCT[24,25], with further evidence suggesting that early behavioral and neural target engagement may be necessary to evoke cognitive gains[26,27]. In those who do show improvement in response to TCT, the durability of cognitive gains may be limited[28], with some effects weakening six months following training, even for individuals who do receive a full therapeutic "dose." Evidence from ongoing studies in our laboratory indicates that treatment adherence is highest in the first 10-15 hours of training (even if required to complete the training in the laboratory), suggesting that novel interventions could capitalize on this early engagement to promote immediate and long-term cognitive improvement. Thus, in order to develop a fully viable clinical treatment, two critical goals must be attained: 1) lessen the duration of TCT necessary to achieve cognitive and neuroplastic gains; and 2) improve the durability of TCT such that cognitive gains may sustain beyond the duration of treatment, influencing long-term cognitive and functional outcomes.

**Neuromodulation has the capacity to enhance TCT**: Transcranial direct current stimulation (tDCS) is a viable neuromodulatory approach with promise for enhancing cognition in SZ. tDCS applies weak (1-2mA) electrical stimulation to the scalp, and is observed to evoke neural excitability and activity by influencing neural resting membrane potentials. Previous work has demonstrated that anodal tDCS reliably enhances motor-evoked potentials in healthy adults[29], and can enhance prefrontal brain activation measured during a verbal fluency task[30]. In patients with SZ, prefrontal tDCS has been shown to elicit improvements in working memory[31] that related to enhanced

prefrontal gamma oscillatory activity[32], suggesting that such an intervention may evoke oscillatory neuroplasticity with pro-cognitive effects in SZ. However, tDCS has also been shown to inhibit psychophysiological responses, which may be the result of "offline" stimulation (i.e. stimulation unaccompanied by a task or goal-directed engagement). For example, a measure of auditory attention (mismatch negativity) and a measure of processing speed were both found to worsen in response to brief offline prefrontal tDCS[33,34]. This suggests that without placing effortful demands on the prefrontal system during stimulation, anodal tDCS could be reinforcing the inherent dysconnectivity consistently observed in SZ[35].

Both TCT and tDCS have independently shown a modulatory influence on prefrontal oscillatory gamma that coincides with cognitive improvement. Similar work in an animal model of SZ showed that cognitive inflexibility corresponded to deficient evoked prefrontal gamma oscillations, but recovered in response to direct prefrontal stimulation in the gamma frequency[36]. Based on this evidence, the current study will combine TCT and tDCS in human patients with SZ to test the hypotheses that: 1) individuals who undergo TCT+tDCS will show improvements in global cognition more rapidly than TCT alone (Aim 1), and 2) that TCT+tDCS will elicit increases in prefrontal oscillatory gamma power that coincide with improvements in global cognition (Aim 2). Though both interventions have demonstrated cognitive benefits independently, their synergistic effects remain unstudied. To date, one study has examined intermittent combined working memory-focused cognitive remediation and tDCS, demonstrating more rapid gains in working memory but no observed improvements in global cognition[37]. Also, previous work in our laboratory demonstrated that gains in auditory processing speed within the first 20 hours of TCT were predictive global cognitive improvement in SZ[27], which may indicate a critical window for inducing long-term neuroplastic and behavioral gains. We will demonstrate that enhanced global cognition after a brief TCT+tDCS is more durable compared to TCT alone (Aim 3).

**Scientific Premise of Exploratory Aim:** Computational approaches will be necessary to identify predictors of neuroplasticity: Cognitive deficits in SZ are characterized by disruptions spanning multiple biological and psychological levels of analysis, including genetic, molecular, circuit, system, and ultimately behavioral units[38]. Computational neuroscience approaches will be necessary to adequately model the complex mechanisms underlying the pathophysiology of SZ, as well as the targeted treatments that may seek to intervene at multiple biological and psychological levels[39]. Previous work has demonstrated that computational methods such as

machine learning have shown great promise for the diagnosis, prognosis, and personalized treatment of various psychiatric disorders[40]. For example, such an approach has been employed on EEG data to predict response to clozapine[41]; expanding on these findings will assist in the identification of biomarkers, and will be necessary to determine treatment efficacy in a personalized medicine approach. This exploratory aim seeks to utilize a similar approach to elucidate the viability of oscillatory biomarkers in addition to clinical characteristics in the prediction of a neuromodulation and cognitive training treatment response. In doing so we will explore whether a machine learning approach demonstrates that gamma oscillatory or functional connectivity patterns can predict treatment response to a TCT+tDCS intervention in individuals with SZ and related psychiatric disorders (Exploratory Aim).

**Significance of the Expected Research Contribution:** This work has critically important implications for treatment in people with SZ and related psychiatric disorders, where cognitive deficits are shown to account for disruptions in functioning. If successful, these findings will elucidate a biological treatment target for cognition in SZ, and lay the groundwork for a new treatment that could be readily deployed in a clinical setting.

**Innovation:** The proposed research is innovative as it examines the neural system and behavioral effects of TCT combined with tDCS. While previous outcomes have been mixed with regards to TCT and tDCS alone, findings from these literatures suggest both treatments may intervene on a common mechanism: prefrontal gamma oscillatory power and prefrontal functional activation. Given the prefrontal cortex's critical role in both sensory and higher-order cognitive processes, as well as evidence from both the human and animal literatures indicating it may respond to neuroplasticity-based interventions, it serves as an ideal neural target for the treatment of cognition in SZ (though we acknowledge that changes in gamma may be governed by cross-frequency coupling with slower oscillatory patterns such as theta). This study is innovative in that it will use an experimental medicine framework to examine target engagement, and determine whether TCT+tDCS can improve the behavioral efficiency and sustainability over either intervention alone. Additionally, we propose exploratory analyses in which we will use a machine learning approach to assess whether baseline psychophysiology and behavior can predict treatment response. This computational psychiatry approach represents an innovative departure from previous work in this field, and will allow us to characterize and model both behavioral and neuropsychiatric mechanisms supporting cognitive recovery in SZ.

*2.2* Preliminary Data:

**Mobile cognitive training drives cognitive and symptom improvement in first-episode psychosis patients:** Our laboratory's previous study asked patients with SZ (mean age 21 years) to undergo either 40 hours of TCT or computer games on laptops at home for 8 weeks[15]. TCT subjects showed significant gains in global cognition, processing speed, and verbal learning/memory, compared to controls (Figure 1, left). We show at 6-month follow-up that the TCT group showed greater improvement in positive symptoms and trend-level improvement in total symptoms compared to controls (Under Review, Figure 1, right). In the current proposal, we aim to see similar effects in a shorter timeframe (20-hours of TCT; 10 hours tDCS; 3-month clinical follow-up).

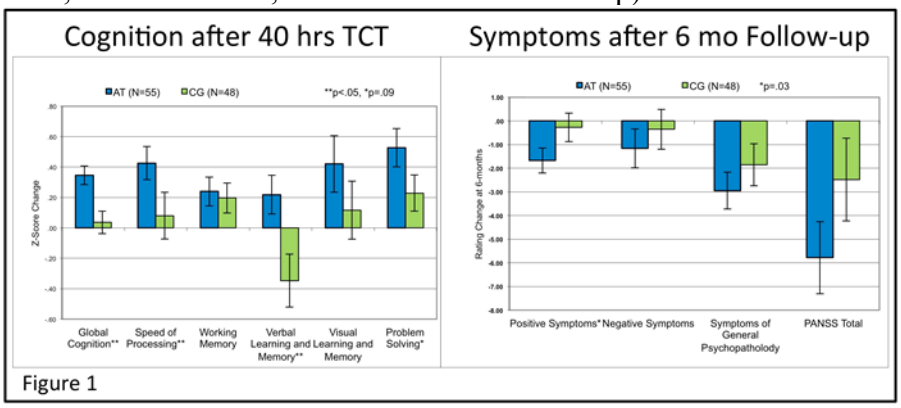
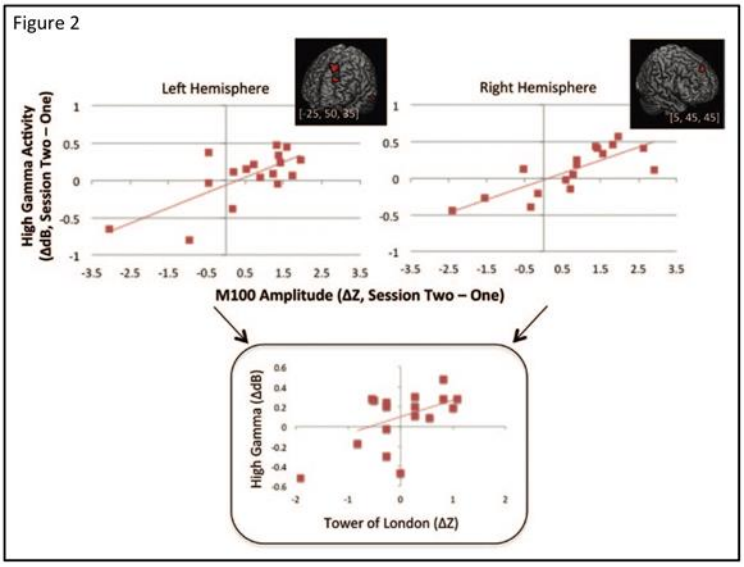
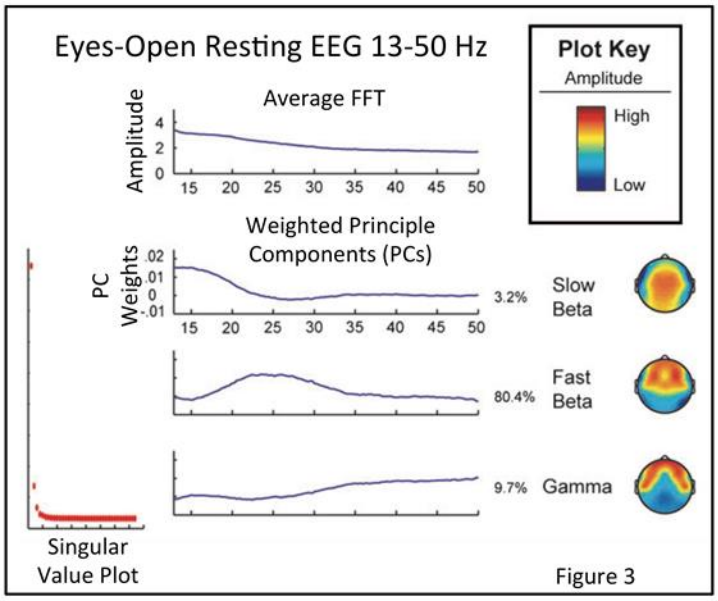


Figure 1

**Cognitive training induces changes in prefrontal gamma power in patients with SZ:** We have previously shown functional plasticity using fMRI and MEG in frontal cortex after training in patients with chronic illness (mean age 40 years)[42,19,22,43]. For example, prior to training, during a simple syllable-identification task, patients show a reduced M100 response in auditory cortex. After training, they show a significant increase in M100, as well as increases in high gamma power in prefrontal cortex (Figure 2). Increased prefrontal high gamma power correlates with gains in M100, and both are associated with improvements in executive functioning. Thus, after training, significantly enhanced gamma-oscillatory power is observed in the prefrontal cortex. In this proposal we ask: Does a TCT+tDCS intervention more rapidly induce changes in prefrontal gamma? Will changes in gamma correspond to changes in global cognition?




**Gamma power is observed during resting EEG in patients with schizophrenia and their relatives:** Findings from our partner group, the Sponheim Laboratory, has previously shown evidence of prefrontal gamma obtained during eyes-opened resting EEG in a sample of SZ patients, patients with bipolar disorder, and their relatives44 (Figure 3). A principal components analysis (PCA) limited to the 13-15 Hz frequency band was found to have 3 primary components, including gamma. The gamma signal was reliably observed in bilateral prefrontal cortex. For the current proposal, in addition to rest, we seek to measure pre- and post-treatment gamma power on a N-back working memory task, and in an auditory oddball paradigm.



**Computational Model Selection and Outcome Prediction in SZ patients undergoing TCT:** In support of the Exploratory Aim, we have employed a model selection and regression approach using the least absolute shrinkage and selection operator (LASSO)[45] on 43 individuals who underwent TCT[15]. We carried out 10-fold cross validation of the LASSO using cognitive, behavioral, and demographic variables to predict cognitive outcomes in response to TCT. This procedure identified lower baseline global cognition, higher baseline education, and gender as variables predictive of increased global cognition following TCT (Ramsay et al., Under Review). We aim to use LASSO and related elastic net models for model selection in our machine-learning approach to determine whether baseline electrophysiology, in addition to cognition, behavior, and demographic variables, is predictive of response to TCT+tDCS. Such an approach has been previously used with EEG[46,47].

# 3.0 Study Endpoints/Events/Outcomes

*3.1* Specific Aims:

- To investigate whether tDCS or Alpha tACS enhances the effect of cognitive remediation therapy on cognition, symptoms, and functional outcomes
- To determine if tDCS or Alpha tACS enhances functional brain activation measured by EEG

*3.2* Specific Hypotheses to be Tested:

- tDCS and CRT will enhance cognitive gains measured by Brief Assessment of cognition in Schizophrenia (BACS) testing over sham tDCS and CRT.
- Alpha tACS and CRT will enhance cognitive gains measured by Brief assessment of cognition in Schizophrenia (BACS) testing over sham tDCS and CRT.
- tDCS and CRT will enhance functional brain activation and connectivity measured by EEG over sham tDCS and CRT
- Alpha tACS will enhance functional brain activation and connectivity measured by EEG over sham tDCS and CRT.

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

*4.1* Description: This protocol will utilize the StarStim Non-Invasive Wireless tCS Neurostimulator (Neuroelectrics, Spain). StarStim is a battery driven multi-channel direct current stimulator that delivers a low current to the outer cortex via small sponge electrodes (surface area of 25cm$^2$), which are placed directly on the scalp. This device is supported for nonsignificant risk clinical trial use in accordance with FDA's regulatory requirements under 21 C.F.R. Part 812 for unapproved devices. For a full description of the tCS

device, please refer to following documents (found in Supporting Documents):

- StarStim User Manual
- Electrodes User Manual
- Safety & IRB Letter
- FDA minimal risk letter

Participants will wear a cap labeled with the 10-20 EEG system of electrode positioning. Prior to placing the cap, the stimulation electrodes will be soaked with a saline solution to minimize the risk of skin irritation. To stimulate the left DLPFC, the anode will be placed over F3, and its corresponding cathode over the right supraorbital region. The current intensity will be 2 mA (total current density over the stimulated area: 0.08 mA/cm2) which is below the threshold for tissue damage. For the active stimulation, the current will be ramped up during the first 15 s to a maximum of 2 mA and maintained for the first 20 minutes of each cognitive remediation session. After the 20 minutes, participants will continue the remaining 40 minutes of training.

A second condition will feature transcranial alternating current at an individualized alpha frequency (~10hz). Using the same electrode positioning (F3 and Fp2), subjects will receive 20 minutes of in-phase individual alpha +1hz sinusoidal stimulation at 1mA.

For the sham stimulation, we will use the same electrode placement and the 2mA tDCS current will be ramped down immediately after ramping up in order to achieve an effective blinding.

The described electrode placement is consistent with previous protocols targeting working memory. (Fregni 2005, Andrews 2011, Gazzaley 2011). This procedure is also in accordance with other protocols that have outlined safe administration (Nitsche 2008). These studies found that across more than 2000 subjects, no major side effects were reported. Minor side effects were found, which included itching under the electrode sponge and occasional occurrence of headache, fatigue, or nausea (Poreisz 2007).

## 5.0 Procedures Involved

*5.1* Study Design: This is a double-blind randomized controlled trial. 105 participants, after signing informed consent and determining eligibility, will be randomized to receive either active tDCS, active tACS, or a sham tCS. *Only 20 participants will be randomized to tACS.*

*5.2* Study Procedures:

After the initial consent form has been signed, participants will undergo an abbreviated MINI, consisting of the mood, mania, suicide, and psychosis modules, to confirm diagnosis. The exception to this is if the participant has completed the MINI or Structured Clinical Interview for DSM-IV or DSM-5 (SCID-IV or SCID-5) for another study within our lab or in a collaborating lab within the last year and has consented to sharing of data with other studies. Collaborating labs include those run by Drs. Sophia Vinogradov, Scott Sponheim, Kelvin Lim, and Angus MacDonald. If a participant is enrolled in the COPRR, study staff can also use diagnostic assessments from the COPRR. In these cases, the diagnosis can be confirmed from the previous diagnostic assessment. Re-evaluation of diagnosis will be made via the abbreviated MINI when the previous evaluation was more than 1 year earlier. They will complete the Columbia-Suicide Severity Rating Scale (C-SSRS). They will also complete the WTAR. Inclusion of the WTAR allows cognitive gain to be analyzed against inherent intelligence. We will ask about handedness using the Edinburgh Handedness Inventory. Throughout one to three additional sessions, participants will complete the BACS, Positive and Negative Syndrome Scale (PANSS), Social Functioning Scale (SFS), Quality of Life Scale (QoLS), Perceived Stress Scale (PSS), COVID-19 Stress Survey, Virtual Reality into the Assessment of Functioning in Clinical Trials (VRFCAT), Dot Pattern Expectancy (DPX), Binocular Surround Suppression, and an EEG evaluation including the N-back, Auditory Steady State Response (ASSR), Mismatch Negativity (MMN), and rest tasks. The WTAR, C-SSRS, and Edinburgh Handedness Scale may be completed during the additional sessions if there is not enough time during the consent visit. This proposed battery would assess cognitive control, cognitive gain, social functioning, working memory, changes in symptoms, and neural plasticity. Inclusion of PANSS and C-SSRS allows researchers to evaluate symptoms and monitor for adverse effects. Medications and substance use, including nicotine, will be recorded during initial evaluation as well. For the Binocular Surround Suppression task, participants will see a series of simple images (e.g., gray stripes) presented on a computer screen and will be asked to make basic judgments about their appearance (e.g., report which of the two images appears stronger). participants will make responses by pressing buttons on a response device (e.g., keyboard). Images will be viewed through a visual stereoscopic display device (like 3D glasses). Participants will be asked to keep their head position stable to focus their eyes at the center of the screen during the task. The task will take approximately 6 minutes. All intake/baseline tasks may be completed over 2-4 visits, depending on each participant's availability. Total intake/baseline appointment time will be approximately 7-10 hours.

The EEG acquisition will rely on a dedicated EEG system located within the ARC which utilizes ePRIME and Presentation software for data capture. EEG recording will be sampled at 1024 hz and carried out from 32 channels, including an array of frontal electrodes including F3, FZ, and F4. The EEG

assessment will examine prefrontal oscillatory activity during multiple tasks, including an Auditory Steady State Response (ASSR) task driving 40hz and 20hz click trains, a Mismatch Negativity (MMN) task with duration and double deviant stimuli, eyes open and eyes closed rest, and the N-Back (2-back version described below). Preparation and recording will take approximately 2-3 hours in total.

After baseline measurements are completed, all patients will participate in cognitive remediation therapy (CRT). Participants will complete between 2 to 4 CRT sessions per week, each lasting approximately 60 to 90 minutes, for a total of 3 to 5 weeks. This study will utilize a commercially available CRT software system. The commercially available software will focus on enhancing sensory processing and working memory. Each CRT session involves an in-session assessment of skill acquisition (Bubble Pop and Sound Sweeps), as collected by the CRT software. The assessment will be completed prior to each CRT session and after its completion.

Patients will be randomized into three arms: active tDCS vs. active tACS vs. sham tCS. In the tDCS condition, stimulation will be applied at a current of 2mA via two saline soaked electrode sponges (25cm2) each CRT session. The anode will be placed over left DLPFC at F3, according to the 10-20 international system for EEG electrode placement. The cathode will be placed over the contralateral supraorbital area. This placement is consistent with previous protocols targeting working memory. In the tACS condition, stimulation will have an identical electrode placement and will be applied at 1hz above an individual's individual alpha peak frequency (defined as the frequency with the highest power in the 7-13hz alpha range measured from resting EEG at baseline). Individual alpha tACS will be in-phase sinusoidal stimulation at 1mA. The sham condition will have an identical electrode placement as both the tDCS and tACS conditions.

After electrodes have been placed, the participants will be instructed to complete their cognitive training via iPad for approximately 60 minutes. The tDCS will be applied at a current of 2mA via two saline soaked electrode sponges (25cm2) for the first 20 minutes of each CRT session in the active condition. In the sham condition, tDCS will be ramped up to 2 mA via two saline soaked electrode sponges (25cm2) over the first 30 seconds of each CRT session and then turned off. The tDCS device will remain in place throughout the CRT session. After completion of the training, the tDCS device will be removed.

Participants will be asked to complete the C-SSRS at the completion of 5 CRT sessions (Mid-Point assessment) and after 10 CRT sessions (End of Intervention assessment). At the End of Intervention assessment,

participants will additionally be asked to complete the EEG assessment (with N-Back, ASSR, MMN, and Rest), PANSS assessment, BACS, SFS, QoLS, PSS, COVID-19 Stress Survey, VRFCAT, Binocular Surround Suppression, and DPX. PANSS and C-SSRS evaluation will be used to determine any change in symptoms and safety for continuing in the study. If the study staff is concerned about an increase in symptoms, they may conduct an additional PANSS assessment at the mid-point assessment. The End of Intervention assessment will take approximately 5-8 hours over 2-4 appointments.

After the 10 sessions of training are completed, we will ask participants about the tolerability of the protocol. At the end of the 1-month follow-up visit we will ask participants if they thought they were in the active or sham condition.

Participants may be asked to return to the ARC to re-administer sessions, if data was missing or of poor quality. If participants need to repeat a visit (e.g., readministration of EEG measures due to loss of data), they may be offered the same compensation for that visit a second time. Offering compensation for repeat visits will be at the discretion of the investigator and may be subject to reason for re-administration (e.g., the participant was intoxicated at their visit). Reasons for offering additional compensation will be documented with notes to file in the participant case files.

**Schedule of Events:**

| Test / Means of Completion | Consent | Baseline | Each Training | After 5 Sessions | After 10 Sessions | 1 Month Follow-Up |
|---|---|---|---|---|---|---|
| MINI / Researcher-led | X[2] | | | | | |
| WTAR / Researcher-led | X[1] | X[1] | | | | |
| Edinburgh Handedness Inventory / Researcher-led | X[1] | X[1] | | | | |
| CRT & tCS sessions / On iPad* | | | X | | | |
| PANSS / Researcher-led | | X | | | X | X |

| | | | | | | |
|---|---|---|---|---|---|---|
| C-SSRS / Researcher-led | | X | | X | X | X |
| BACS / On iPad | | X | | | X | X |
| EEG (N-back, ASSR, MMN, & Rest) / On computer | | X | | | X | |
| SFS & QoLS / Self-report on iPad* | | X | | | X | X |
| PSS / Self-report on iPad* | | X | | | X | X |
| VRFCAT / On iPad | | X | | | X | X |
| DPX / On computer | | X | | | X | X |
| Tolerability Questionnaire / Researcher-led | | | | | X | |
| Blinding Question / Researcher-led | | | | | | X |
| Binocular Surround Suppression Task / On computer | | X | | | X | |
| COVID-19 Stress Survey / Self-report on iPad* | | X | | | X | X |

[1] WTAR and Edinburgh Handedness Scale will be completed at either the consent or baseline visit

[2] Unless able to confirm diagnosis from diagnostic assessment from previous study (within last 12 months)
* Can be completed on an alternative device, if necessary.

**COVID-19 Adaptations:** Due to the ongoing COVID-19 pandemic, the following modifications to study procedures may be used to mitigate pandemic-related risks while participating in this study.

- All study procedures that can be completed remotely will be completed remotely, if possible. Affected assessments are listed below.
    - MINI
    - WTAR
    - Edinburgh Handedness Inventory
    - PANSS
    - C-SSRS
    - SFS, QoLS, & PSS
    - COVID-19 Stress Survey
    - Tolerability Questionnaire
    - Blinding Question
    - Demographics
    - Some parts of the BAC (will primarily be done in person because some sub tests cannot be done remotely)
- Certain in-person procedures may be forgone in certain cases. For example, if a participant becomes ill when they are well into the course of the study intervention, the remaining CRT sessions and in-person Post-Training assessments can be forgone. If the PI deems it to be safe to collect those data at a later date, the participant may be asked to complete the missed assessments.
- Study staff will allow participants to complete 2 CRT sessions at each appointment, if desired, in order to limit overall frequency of appointments. Participants will still be asked to complete 2-4 CRT sessions per week. These can be completed in 1-4 appointments per week, depending on the number of CRT sessions per appointment.
- All participants will be screened for COVID-19 symptoms before any necessary in-person appointments. In general, the screening will assess risk through questions about symptoms, exposures to infected people, and high-risk behaviors (e.g., attending large events without precautions). Some questions will be optional, and will only be administered during high levels of community transmission (per CDC) or at staff discretion; the PI will make a determination whether the visit may continue if these optional questions are answered yes. The complete screening can be found in the COVID-19 Screening document. Participant temperatures will also be taken before each EEG to confirm it is not higher than 100.4 degrees Fahrenheit. Documentation of a temperature =< 100.4 will be kept, but the exact temperature will not be recorded.

- As described in the Ramsay Lab Sunrise Plan, all participants will be required to wear a face mask during all in-person procedures. There will be some procedures that participants are not able to wear a mask (e.g., during an EEG).

*5.3* Follow-Up: Participants will return for repeat testing approximately one month after the end of treatment. Assessment with the BAC, SFS, QoLS, PSS, COVID-19 Stress Survey, VRFCAT, DPX, PANSS, and C-SSRS will occur at follow up. The final set of tasks should take approximately 3-4 hours over 1-2 visits.

*5.4* Individually Identifiable Health Information: This protocol will involve the collection of Individually Identifiable Health Information.

- Full names, phone numbers, and addresses will be collected to maintain contact with the research participants.
- The participant's name and mailing address will be used for compensation.
- Email addresses will be collected from participants who consent to receiving either study related and/or compensation related communications via email.
- Date of birth will be requested to determine eligibility for the trial. Age at time of participation will be used in data analysis.
- Service dates for study appointments will be included in study records.

Contact information will be stored in a secure dedicated folder in Box. Only qualified, trained study team members who require access to this file will be provided with access. Date of birth will be requested during the interview to confirm eligibility. Dates of study appointments will appear in the study files. All study data in binders and in REDCap will be completely de-identified. Participants will be registered in OnCore, which will include their name and date of birth. If the participant is a Fairview patient, their Medical Record Number (MRN) will also be associated with their registration in the OnCore portal.

## 6.0 Data and Specimen Banking

*6.1* Storage and Access:

All data management servers will meet all relevant privacy and security standards for electronic clinical trial data entry as storage, as well as HIPAA standards for confidentiality and privacy.

Access to study data, particularly data with identifying information, will be limited to individuals listed on the delegation of authority log, or those who have authority to review study records. Identifying information will not be shared outside of the UMN study team unless required by law. Study staff

will only be provided with access to the study data that they need to perform their work duties.

All identifying information will be maintained for a minimum of six years after the completion of the study in compliance with HIPAA regulations. Any data use agreements that allow for the sharing of study data will be maintained for a minimum of two years past their expiration.

For a visual representation of the flow of study data, please refer to Appendix 1.

**Consent documents:** Consent documents, including HIPAA Authorizations and UBACC assessments, will be collected and stored in REDCap. Historic consent documents that were previously collected on paper will be stored with the physical regulatory files in a locked cabinet in a locked office. If need be, participants may still complete paper consent documents. Copies of physical consents will be uploaded into a dedicated folder within Box. Locations of the consent forms will be documented within the regulatory files and OnCore system. These records will only be made available to study staff and will not be shared with any collaborators. Identifying information will not be shared outside of the UMN study team unless required by law.

**Assessment data:** Some study data will be collected in physical forms, namely the MINI, PANSS, and miscellaneous notes captured during the assessment appointments. These documents will be kept in a locked drawer in a locked office space until they can be scanned to the Box folder. Each participant will have a separate folder in Box and all study files will follow a naming convention to identify participant, assessment, and time point.

The DPX task may be completed on an AHC-IS supported laptop or the same computer listed in the EEG Data section below. The EEG-dedicated computers are not managed by AHC-IS, as the AHC-IS management software would potentially interfere with the sensitive communications between the devices and the EEG instruments. However, per the agreement with AHC-IS, these devices are not connected to the internet or another other devices, are not used for any purpose other than EEG collection, and do not process or store any PHI. If the DPX task is completed on an AHC-IS supported laptop, the data will be uploaded directly to Box for long-term storage. If the DPX task is completed during the EEG appointment on the psychophysiology lab computer, the data will be transferred via flash drive to the study team's desktop computer, where it will be uploaded to Box for long-term storage. After the data is uploaded to Box, it will be deleted from any devices it remains on (computers, flash drives, etc.).

The Binocular Surround Suppression task will be completed on the same computer listed in the EEG Data section below. The EEG-dedicated computers are not managed by AHC-IS, as the AHC-IS management software would potentially interfere with the sensitive communications between the devices and the EEG instruments. However, per the agreement

with AHC-IS, these devices are not connected to the internet or other devices, are not used for any purpose other than EEG collection, and do not process or store any PHI. The data will be transferred via flash drive to the study team's desktop computer, where it will be uploaded to Box for long-term storage. After the data is uploaded to Box, it will be deleted from any devices it remains on (computers, flash drives, etc.).

Two assessments, the VRFCAT and BAC app, will be collected using technology developed by VeraSci (previously NeuroCog Trials). These assessment data will be stored directly onto servers maintained by VeraSci. The BAC App will be delivered on an iPad registered with AHC-IS, and the VRFCAT will be delivered on an iPad or a laptop managed by AHC-IS (depending on the version the developers provide access to). No assessment data will be stored on the devices. By design, the assessments will not collect direct identifiers, though it will store the date of data collection. All assessment data will be collated underneath the participant's unique study ID number. Outcome data from the BAC and VRFCAT will be transcribed into a REDCap database in regular intervals by study staff. At the end of the trial and during interim analyses, study staff will extract all performance data for both the VRFCAT and BAC assessments for storage in Box. VeraSci will maintain records of all data generated during this study to use for their own purposes. License Agreements and a DUA exist between the University of Minnesota and VeraSci to this end; as the instruments do not collect PHI by design, VeraSci declined to enter into a BAA with UMN.

Performance data from BrainHQ cognitive assessments and training will be collected on the BrainHQ app and stored on secure servers hosted by Posit Science Corporation. Data will be collected on an iPad managed by AHC-IS. No data will be stored on the device. All data will be collated using a unique study identification number and will not contain direct identifiers. Outcome data from the cognitive assessments will be entered into the REDCap database for this project. During interim analyses and at the end of the trial, study staff will extract the trial-by-trial and outcome data for both assessments and training from the BrainHQ website and store this data in Box for further analysis. Posit Science will maintain records of all data generated in this study to use for their own purposes. A BAA exists between Posit Science and the University of Minnesota Department of Psychiatry to allow sharing of this data.

All other assessment data will be collected directly into the REDCap database during assessment appointments. AHC/HST-managed devices will be used to collect this data for in-person appointments. Any assessments collected in REDCap during a remote appointment will be completed using a participant-owned device. Data from the REDCap database will be extracted to Box during interim analyses and at the end of the project for final storage. The data will remain in Box indefinitely.

All eCRFs will be reviewed by secondary staff to check for omitted data and data inconsistencies. Once data entry is confirmed correct, the record will be locked to prevent changes. Each data record will be evaluated regularly for errors. If errors are discovered, the record will be unlocked and the data corrected. An audit trail will be created and will allow recovery to any point in the change log if required. Once the data entered from scanned forms have been verified for accuracy and clarity, the documents will be shredded. Assessment data will contain no direct identifiers by design, though they will contain the date of data collection.

If digital assessments are not available, paper/pencil or alternate online versions of the assessment will be used when possible. Study staff will upload or transcribe data to final storage location (e.g. REDcap) when available. Paper records will be kept in locked cabinet in locked office until date of destruction.

**EEG Data:** EEG data will be collected on dedicated computers located in the Department of Psychiatry Ambulatory Research Center using E-PRIME software. These computers are not managed by AHC-IS, as the AHC-IS management software would potentially interfere with the sensitive communications between the devices and the EEG instruments. However, per the agreement with AHC-IS, these devices are not connected to the internet or any other devices, are not used for any purpose other than EEG collection, and do not process or store any PHI. Data from EEG assessments is taken from these devices via flash drive to the study team's desktop computer, where it is stored locally on the hard drive. The data will also be uploaded to the CMRR (Center for Magnetic Resonance Research) Secure Server. Both the dedicated EEG computers and the flash drive are regularly wiped of participant data. By design, the EEG assessment does not collect any direct identifiers, though it does store the date and time of assessment. The EEG computers, the flash drive, and the staff desktop computer are kept in locked offices in the Department of Psychiatry.

**fMRI Data:** Previously collected fMRI data will be stored and analyzed at the Center for Magnetic Resonance Research (CMRR), which is part of AHC-IS. De-identified images are initially stored on the computers used to collect the data (these are routinely wiped of participant data), before being transferred to the CMRR's secure servers. All long-term data storage and analysis will be managed on the CMRR secure servers or MSI servers. Any additional behavioral data collected during the scans will also be stored in Box.

**Other Study Data:** As part of the consent process, participants will be asked to share their contact information, including their full address, phone number, and email address with study staff. Participants will also be asked

whether study staff may contact their primary treating clinician to discuss their involvement with the study and safety concerns. This information will all be collected in a form in REDCap. Only qualified UMN study staff will have access to these forms.

An enrollment log containing the participants' personally identifying information, including name and contact information, will be stored in Box in a dedicated study folder. Only qualified UMN study staff will have access to the study folder. This enrollment log will also maintain the key between subject ID numbers and personal identifiers. A separate randomization table will indicate which participant IDs were placed in each condition.

Additionally, participant identities, date of birth, demographic data, and date of consent(s) will be maintained in OnCore. If the participant is a patient in the Fairview Clinics, their medical record number will also be associated with their account in OnCore. These records will be maintained for a minimum of six years after completion of the study.

Text messages sent to and from participants will temporarily be stored on a University cell phone. The cell phone will not store the participant's name in the contact list of the device; study staff may store the participant's number under their study ID code in order to recognize them during text conversations. When the participant has completed the study or withdraws, their contact information will be deleted from the phone. The cell phone will remain on University property, unless it is being taken home by a coordinator for the purpose of contacting a participant for an appointment scheduled outside of business hours (Mon-Fri 9AM-5PM). For example, if a coordinator had an appointment with a participant on Saturday, the coordinator could take the phone home with them on Friday night to confirm the participant's attendance at the appointment before commuting to the University on Saturday. When the cell phone is not in use, it will be stored in a locked cabinet in a locked office. The phone will be locked with a passcode and will not have pop-up messages enabled on the locked screen; study staff will need to unlock the phone and navigate to the messages to read the contents of any texts received by participants. Text messages will be regularly deleted from the cell phone (at least weekly) to protect participant PHI. If the text messages are of significant concern (e.g., indicate a safety issue), the contents of the messages will be saved for future review, using screenshots of the conversation. The phone number/identification of the participant will be redacted from any transcripts.

Participants may email study staff with questions or concerns, or to make arrangements for study visits. Emails with participants will be saved during the course of the study and will be deleted with other identifiable information. If deemed significant and relevant to the participant's study record, de-identified emails may be saved to the participant's study file in Box. To de-identify emails, all direct identifiers (name, email address, date of birth, etc.) will be redacted from the email in PDF format. Study staff will

place black bars over any directly identifying information. The redaction will be verified by a secondary staff member for accuracy and completion to ensure patient privacy prior to upload into Box for permanent storage. The dates of communication will be maintained in the emails to provide context for the conversation.

*6.2* Data:

- Wechsler Test of Adult Reading (WTAR)
- Edinburgh Handedness Inventory
- Brief Assessment of Cognition in Schizophrenia (BACS)
- Social Functioning Scale (SFS)
- Quality of Life Scale (QoLS)
- Perceived Stress Scale (PSS)
- COVID-19 Stress Survey
- Virtual Reality into the Assessment of Functioning in Clinical Trials (VRFCAT)
- Dot Pattern Expectancy (DPX)
- Binocular Surround Suppression
- Positive and Negative Syndrome Scale (PANSS)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Cognitive Training Performance Data
- EEG Data (with N-Back, ASSR, and MMN performance data)
- fMRI Data (including structural and functional images) and related behavioral data (no longer collecting this data)
- Protocol Tolerability Questionnaire
- Blinding Reliability Question

*6.3* Release/Sharing: Data generated by Posit Science and VeriSci applications will be collected and maintained by these institutions and may be used to perform analyses in preparation of manuscripts, presentations, and other dissemination of results to the public, as well as for quality improvement and program development, as is seen fit by these companies. They will maintain these records indefinitely. Data collected by these applications will not contain direct identifiers by design, but will contain the date of data collection.

Assessment data may be shared with outside collaborators, provided that there are appropriate data use agreements in place. Before sharing Posit Science or VeriSci data, the PI will verify that they approve the use of their data by another party, and help to establish any necessary agreements

between all parties. Any data that is shared with an outside collaborator will not contain any direct identifiers. Most likely a limited data set will be shared (e.g., assessment dates will still be included), but the data set may be completely de-identified if required by the data use agreements. Data will preferentially be shared via a data shelter managed by AHC-IE, but collaborators may be allowed to access the data in other means if necessary. The exact methods of access and data shared will be detailed in the data use agreements struck between the interested parties

EEG data may be shared with outside collaborators, much like with assessment data. If necessary, the PI will enter into a data use agreement with the collaborators to ensure the participant data is protected. Participant identifiers will never be shared with the EEG data. Though the data will most likely be shared as a limited data set (e.g., date of assessments will be included), the data set may be completely de-identified if required by the agreements. Data will preferentially be shared via a data shelter managed by AHC-IE, but collaborators may be allowed to access the data in other means if necessary. The exact methods of access and data shared will be detailed in the data use agreements struck between the interested parties.

## 7.0 Sharing of Results with Participants

*7.1* Individual and group results 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 Duration

*8.1*

- An individual will be enrolled in the study for approximately two to three months total to provide complete data.
- We anticipate requiring five years to enroll all subjects needed for this trial
- After all subjects are enrolled, it will take approximately six months to finalize data collection and data entry. Data analysis will require another year to complete.

## 9.0 Study Population

*9.1* Inclusion Criteria:

- Meet diagnostic criteria for schizophrenia or schizoaffective disorder
- Are age 18-64
- Fluent in written and spoken English
- Have an outpatient status of at least 1 month prior to participation

- Has been on a stable dose of psychiatric medication for at least one month prior to participation (titration to a lower dose of psychotropic medications under supervision of a psychiatrist can be allowed at the discretion of the investigators)

*9.2* Exclusion Criteria:

- History of seizures or epilepsy
- Metallic cranial plates, screws, or implanted devices
- History of craniotomy
- History of stroke
- History of eczema on scalp
- Pre-existing sores or lesions at sites of tDCS electrode placement
- Non-removable facial piercings
- Current or possibility of current pregnancy
- Active suicidal ideation at screening or baseline assessments, or previous intent to act on suicidal ideation with a specific plan, preparatory acts, or an actual suicide attempt within the last 3 months, as indicated by the C-SSRS
- In the last 12 months, has received a clinically meaningful dose of a targeted cognitive training intervention as determined by the PI
- WTAR standardized score below 70

*9.3* Screening: Individuals interested in participating will be screened using a series of questions probing for inclusion and exclusion criteria. The phone screen is included in the Recruitment Resources in ETHOS. Additionally, participants will undergo an exam of the scalp prior to tDCS administration to ensure that there are no lesions or sores at the stimulation site.

## 10.0 Vulnerable Populations

*10.1* 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

*10.2* Adults lacking capacity to consent and/or adults with diminished capacity to consent:

One of the hallmark features of psychotic illnesses is diminished cognitive functioning. Despite remarkable advances in psychiatry and neuroscience, there are relatively few treatments available for cognitive deficit. This research project is examining a potential treatment for cognition in psychotic illnesses; therefore, it is necessary to include individuals with diminished cognitive functioning to evaluate the effectiveness of the proposed therapy. This study is a minimal risk trial and those with diminished cognitive functioning will not face greater risks by participating. However, all participants must have capacity to provide informed consent at enrollment and throughout the study. Please refer to section 21.2 for the procedures to determine capacity to consent.

*10.3* Additional Safeguards:

Some of the participants in this study may be patients of the investigators, Drs. Sophia Vinogradov and Ian Ramsay. Other participants may have this study introduced to them by their clinical care team at the partnered recruitment sites. To mitigate the possibility of coercion upon their patients, potential participants from the UMP Outpatient Psychiatry Clinic and Mental Health Neuromodulation Clinics interested in research opportunities may first communicate with the Department of Psychiatry's Clinical Research Recruitment and Outreach Specialist, a neutral third party who will inform the patient of any study they potentially qualify for. If the patient is interested in learning more, the Outreach Specialist will introduce them to the study team, if possible, or collect their contact information to provide to the study team. If the Outreach Specialist is unable to meet with the interested party, another member of the research team will meet with them to discuss the study. All consent discussions will be conducted by study staff and not the investigator/clinicians.

## 11.0 Local Number of Participants

*11.1* Local Number of Participants to be Consented: Approximately 85 participants will be enrolled. Approximately 68 participants are needed to support well-powered data.

## 12.0 Local Recruitment Methods

*12.1* Recruitment Process: We will utilize recruitment flyers posted in the community and in the UMP Psychiatry Outpatient Clinic recruitment areas. We will also have postings on clinicaltrials.gov, Craigslist, vinogradovlab.com, the UMN Department of Psychiatry website, and StudyFinder that will allow participants to self-identify for this study.

All outpatients seen at the UMP Psychiatry Clinic or Mental Health Neuromodulation 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.

When possible, study staff will place physical and electronic postings and make in-person and/or telephone announcements at community mental health support, advocacy, and service agencies.

The Psychiatry Department has hired a Clinical Research Recruitment and Outreach Specialist 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 Specialist 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 Specialist 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 Specialist 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 Specialist 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.

We will utilize the Consortium of Psychosis Research Recruitment (COPRR) in the Department of Psychiatry& Behavioral Sciences. COPRR provides research participants 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.

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.

*12.2* Source of Participants:

- Current patients at the UMP Psychiatry Clinics
- Patients entered into the Psychiatry Recruitment Registry
- Participants entered into the COPRR
- Former participants or individuals who failed phone screens who have agreed to be contacted for further research opportunities
- Self-identifying individuals from the community
- Patients from other partnered recruitment sites

*12.3* Identification of Potential Participants:

Patients who are receiving clinical services for psychotic illness at UMP Psychiatry Clinics or other recruitment sites may be referred to this study if the treating clinician believes they are stable enough to participate in a research study. At UMP Clinics, patients will first be referred to the Clinical Research Recruitment and Outreach Specialist, who will make initial contact. At other partnering clinics, participants will be provided with contact information for the study staff, and the referring clinician may ask permission to share the patient's contact information with the study staff.

The Outreach Specialist has collected a list of patients who have signed the Consent to Contact for Research form, which includes their contact information and basic demographic data to determine eligibility. This list will be made available in Box for study staff involved with recruiting participants. First contact will be made by study staff.

The lab has their own registry of former participants or individuals who failed phone screens, which includes basic demographic information. Any individual in this list who meets basic eligibility criteria may be contacted for this research by study staff.

*12.4* Recruitment Materials:

- Flyer, Contact card
- Clinicaltrials.gov and Study Finder posting
- Website posting

*12.5* Payment: Compensation will be provided to participants in the form of reloadable gift cards hosted by ClinCard (GreenPhire). Participants will receive compensation when they have completed the assessment and training appointments. When a payment is uploaded to the card by research staff, participants will receive a notification by text and/or email if they have opted into this service. Participants will be notified that they will need to disclose personally identifying information, such as their name and address, in order to be registered in the ClinCard system. Participants will be compensated for their time and effort on the following schedule:

- Consent and Diagnostic Assessment: $15
- Baseline assessment completion: $85
    - Clinical assessment: $45
    - EEG assessment: $40
- tDCS treatment sessions: $20 each @ 10 appointments = $200
- End of Treatment assessment completion: $85
    - Clinical assessment: $45
    - EEG assessment: $40
- 1 month follow up assessment: $45
- Total compensation earned: $430

If participants do not complete all of the Baseline or End of Treatment assessments, they will receive pro-rated payments based on the components they were able to complete. If participants are asked to re-do any appointments (e.g., re-administration of EEG due to poor signal quality), they may receive the same compensation for that visit a second time. Decisions to compensate for a visit the second time will be up to investigator discretion and may depend on the reason for readministration (e.g., the participant was intoxicated at their visit).

Reimbursement for parking:

- Participants may be offered discount tickets to pay for their appointment parking expenses if they park in the ramps at the Fairview hospital location. The vouchers dispensed to participants will be valid for time increments closest to, but not less than the length of their appointment, also accounting for time to get to and from their vehicle and time spent waiting near reception (e.g., "Up to 3 ½ hours" voucher for a 3 hour appointment). Study personnel will not be able to compensate participants for any additional time spent parked in the ramps.
- For other modes of transportation, up to $100 per participant can be reimbursed for public transportation or rides to appointments (taxi, Uber, Lyft, etc.) throughout the study. Receipts will be required for reimbursement of transportation costs and payments will be made on an as-needed basis, totaling up to $100 per participant.

## 13.0 Withdrawal of Participants

*13.1* Withdrawal Circumstances:

- If the participant's PANSS Score increases by 25%, they will require clinical review before continuing. If their score increases by 50%, they will be removed from the study. A 25% PANSS change corresponds to a "minimal" change in CGI. A 50% PANSS score change corresponds to a "moderate" change in CGI. (Leucht et al, 2005).
- If at any time point a participant displays suicidal ideation with a rating of level of 4-5 on the C-SSRS, the participant will require a clinical evaluation. Should any suicidal behaviors emerge at any point during the study, the participant will also require a clinical evaluation. If in the opinion of the study team it is unsafe for them to continue in the trial, they will be removed. Crisis protocol will be followed, which may involve escorting the patient to the emergency room.
- If the participant is unable to tolerate the tDCS stimulation, they will be withdrawn from the study.
- 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 incarcerated or hospitalized (deemed by the PI to be potentially related to study procedures) they will be removed from the study.
- If the participant is not compliant with study procedures, they may be removed from the study at the discretion of the PI.

*13.2* 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.

## 14.0 Risks to Participants

*14.1* Foreseeable Risks:

- Intervention risks: There are no known significant risks associated with the application of tDCS or tACS to date (Bikson et al. 2016; Brunoni 2011). Adverse effects of tDCS and tACS are minor and may include headache, nausea, fatigue, itching, discomfort, burning sensation, and dizziness, and a flashing sensation (phosphenes).

- Risks of Assessments and Batteries: As with all assessments, there is the potential that we will ask questions that make the participant feel uncomfortable, embarrassed, or stressed. We will remind participants that they only need to provide the information that they are willing to answer and can ask to skip questions at any time. In addition, due to the length of the assessment visits, it is possible that participants can feel fatigued or stressed by the interview. We provide the option to split the assessment batteries over several visits in 1-2 week period to reduce the burden on the participant, and we will invite them to take short breaks in the middle of sessions to prevent fatigue.

- Risks of Computerized Training: Participants may become frustrated or fatigued when participating in their computerized training program. To mitigate these risks, we limit the time to 60 minutes per training session. Additionally, they may take breaks in their training sessions if they need to. The programs are self-adaptive to adjust difficult level to approximately 80% success rates for individuals, which should help prevent feelings of frustration during the training programs.

- EEG Risks: During electrode placement, the possibility of skin irritation from contact with the conductive gel exists. However, this is unlikely since the salt concentration of the gel is similar to that of human sweat. There is also a risk of abrasion to the scalp when applying the conductive gel to the electrodes. The gel applicator can feel rough and uncomfortable to sensitive skin. The administrator will check in with the participant regularly to make sure there is minimal discomfort during this process.

- Randomization Risks: Since participants are randomly assigned to their treatment arm, they may receive treatment that is less effective

or has more side effects than the other study treatment, or other available treatments. However, the risks of randomization are minimal and not greater than minimal risk.

- Confidentiality Risks: Participation in research will involve a loss of privacy due to the nature of the questions that are asked during assessment visits and data collected during training sessions. However, records will be handled as confidentially as possible. All participants will be assigned a unique study identifier that will be used to label all of their records. A link will be maintained on a private Box secure server accessible only to specific study staff listed in the Delegation of Authority log. This link will connect the participant's identifying information, such as name, etc., to their assigned ID number. No identifying information will be used in any report or publications that may result from this study. All study records will be kept in secure databases such as REDCap, OnCore, or Box. Paper records will be kept in locked cabinets in locked rooms. Data generated during training or assessments on Posit Science's secure web page will be de-identified and will be available for export for analysis. Identifying information will not be maintained with study records. All members of the study team will be current with their HIPAA, CITI, GCP, and IRB trainings to ensure full compliance with confidentiality laws.

- Email Risks: Participants will be able to opt-in to communicating with study staff via unencrypted email to arrange their appointments and receive study instructions. There are risks associated with email communication, and these risks increase when the emails are sent without an encryption service. Risks of sending or receiving emails without encryption include, but are not limited to:
    - Others can intercept messages
    - If messages are sent or received on an employer-owned device, the employer may have the right to save and read the messages. The internet or cell-phone provider may also have the right to save and read email messages.
    - A copy of the message may be saved on a device or computer system, even if it is deleted.
    - If an email address is not typed correctly, it can be sent to the wrong person
    - Emails can spread computer viruses.
    - Others may be able to access messages on devices that were lost, stolen, or thrown away.
    - If a user changes emails without notifying study staff, they may miss communications.

Emails that are sent to and by the study team will be saved as part of the participant's study record. The emails will be protected as they are with other study records. Emails will be redacted to remove personally identifying information if they are downloaded or saved from the original email account. All personally identifying information such as name and email address will be removed. A second individual will verify the removal of all personally identifying information prior to upload in Box for permanent storage.

Participants do not have to opt-in to email communication in this study. If they change their mind about communicating via email at any time, they can notify study staff about their preferences to communication. If the participant would like to start using email during the study, they will need to sign an email communication consent form.

- Risks of Text communication: Participants may opt in to communicating with study staff via texting a University-owned cell phone to arrange study appointments and receive other study updates. There are risks associated with text communication, including but not limited to:
    - Others can intercept messages
    - If messages are sent or received on an employer-owned device, the employer may have the right to save and read the messages. The internet or cell-phone provider may also have the right to save and read messages.
    - A copy of the message may be saved on a device, even if it is deleted
    - If the phone number is not typed correctly, it may be sent to the wrong person
    - Others may be able to access messages on devices that were lost, stolen, or thrown away
    - If a user changes phone numbers without notifying study staff, they may miss communications.

  Participants will be notified that the phone will only be monitored during business hours (Mon-Fri 9AM-5PM), unless they have an appointment scheduled outside of those hours. They will be informed that they should not use this phone as an emergency contact number as well. Texts that are sent to the study phone will be regularly deleted, unless they are found to be significant to the participant's study record or safety. In this case, screen shots of the texts may be saved and redacted to protect privacy. Study staff will not store the participant's name in the contact log. Their number will be saved with their study ID code so study staff

may identify them during conversations; once the participant completes participation in the study, their contact will be deleted.

Participants do not have to opt into text communication in this study. If they change their mind about communicating via text, they can notify staff at any time about their communication preferences. If the participant would like to start using text during the study, they will need to sign a text communication consent form.

- Some participants in the study may experience worsening psychotic symptoms during their participation. If a participant is hospitalized for psychiatric symptoms, their case will be individually reviewed by the PI. If the hospitalization does not appear to be caused by the study intervention, it will be considered a risk associated with a pre-existing condition and will not be reported to the IRB as an SAE. All hospitalizations will be recorded in the study files and will be available for review by study monitors.

- **COVID-19 Risk:** We imagine the risk of COVID-19 infection while participating in this study to be no more than the risk presented during an average trip to the grocery store. Extensive precautions will be taken, including staff monitoring for risk factors (symptoms, exposures, high-risk encounters, temperature checks), participant COVID-19 screening, required face mask use (participants and staff), required hand hygiene (participants and staff), required social distancing when possible, required additional PPE when social distancing is not possible (face shield, gloves, disposable gown [EEG only];staff only), and extensive disinfection procedures. More specific details about risk mitigation can be found in the Ramsay Lab Sunrise Plan and Recommendations for ARC EEG COVID-19 documents.

## 15.0 Potential Benefits to Participants

*15.1* Potential Benefits: There are no direct potential benefits of this study to participants. If the experimental condition proves to be beneficial to schizophrenia subjects as a group, then this will be extremely helpful in the design of future remediation programs for patients.

## 16.0 Data Management

*16.1* Data Analysis Plan: Our statistical analysis plan is to use a 2 (Between Group: Sham, Active) x 2 (Within Group: Time - pre-tx, post-tx) mixed ANOVA and test for a Group difference and an interaction between Group and Time.

*16.2* Power Analysis: To our knowledge, this is the first study to assess improvement in both cognitive measures and EEG when CRT is coupled with tDCS. A recruitment goal of 105 patients has been set. In this pilot

study, we propose to collect preliminary data to determine effect sizes for power calculations for future studies.

*16.3* Data Integrity: Missing data will be handled in two ways. First, any subject who discontinues the study prior to completion will be replaced by the next eligible subject. The number of subjects dropping from each treatment group will be analyzed at the end of the study to assess possible differences in retention rates between the three conditions. Other potential sources of bias will be assessed between-groups, such as differences in the adherence to treatment and baseline demographic characteristics. Second, if individual tests or interview items are not completed, multiple imputation techniques will be used to predict missing values. These will be based on methods appropriate for longitudinal responses (69). In our lab, schizophrenia subjects who have not dropped out of prior studies have had less than 5% of the above measures missing. For this reason, imputation of missing values has typically shown negligible effects on the means, variances, and correlations of outcome measures. In the case imputation is deemed necessary, results with and without imputation will be reported.

## 17.0 Confidentiality

*17.1* Data Security:

All digital records will require a username and password to access study information. The UMN will utilize a combination of Box, REDCap, and OnCore to store study data for this project, as well as AHC-IS managed devices. The servers maintained by Posit Science are HIPAA compliant, secure servers that will require permissions from the study team to access. VeriSci (formerly NeuroCog Trials) also operates on secure servers, but it is unknown if their servers meet HIPAA standards; however, by design, the data stored on this database will not contain any direct identifiers. The UMN has entered into agreements with both Posit Science (BAA) and VeriSci (DUA) to allow for the use of their software and the data generated.

Any physical records will be maintained in locked cabinets in locked offices, until such time as the documents may be shredded in secure shredders. Access to these cabinets will be limited to the study team.

Direct identifiers will not be included within assessment data or app performance data by design. Direct identifiers will be maintained in consents and participant registries, which will be maintained separately from study data. Date of birth will be captured in the REDCap database in demographics; however, it will be flagged as an identifier and will not be extracted from the database for use in any analyses. Only participant's age at time of assessment will be extracted from the REDCap database.

Participants will be registered within the ClinCard Greenphire payment system to receive their study compensation. Individually identifying information such as the participant's name and address will be included in

this registration. ClinCard Greenphire is a HIPAA compliant system and is an approved payment method for the University of Minnesota.

When participants are registered in OnCore using their Medical Record Number, their EPIC Medical Record will indicate that the participant is enrolled in this study. However, a copy of their consent form will not be placed in their medical record. Clinical staff can obtain contact information for the study staff using the enrollment information in EPIC, if need be. No study information will be included in the participant's employment or education records.

For a description of how data is collected, stored, and shared, please refer to Section 6.0 Data Banking.

## 18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

*18.1* Data Integrity Monitoring: Performance on all measures will be scored, submitted to the database, and monitored for accuracy and integrity. We will regularly conduct data audits to ensure the accuracy and completion of all data. Data sets will be locked once the information is verified as complete and accurate, and an audit trail will be available for all changes to data within the database with the capacity to restore to the original entry if necessary.

*18.2* Data Safety Monitoring:
This is considered a minimal risk trial and we do not anticipate any adverse events from participation in the study. Nonetheless, we will review all unanticipated problems involving risk to participants, serious adverse events, and any participant deaths associated with the protocol. The PI will review all cases and make a determination as to the severity of the adverse event and its relation to study procedures, if any. Reports for events determined to be related to study procedures, those that are unanticipated, or those that are related to participant death will be promptly reported to the IRB.

Study participants who become injured or ill as a direct result of the participation in the study will be able to seek regularly medical care, as needed. Should the study staff learn that a participant is experiencing suicidal ideation, or if they appear to have an increase in psychiatric symptoms, they may elect to make a mid-point assessment with the UBACC, C-SSRS, or PANSS to determine participant safety. If a participant makes study staff aware of active suicidal ideation (e.g., a score of 4-5 on the C-SSRS), study staff will inform Dr. Ramsay immediately, who will perform a safety evaluation (in-person or remotely, as appropriate) as soon as possible. If the Dr. Ramsay is not available or cannot be reached, study staff will reach out to Dr. Vinogradov. If deemed clinically necessary,

the PI may elect to remove participants from the study if they find it is no longer in the participant's best interests to continue participation in the study.

We will follow guidelines for medical devices in the reporting of adverse events in this trial, which defines unanticipated adverse device effects (UADEs) in the Code of Federal Regulations in 21 CFR 812.3(s) as any serious adverse effect on health or safety associated with a device.

## 19.0 Provisions to Protect the Privacy Interests of Participants

*19.1* Protecting Privacy: During all assessment appointments, participants will be reminded that their participation in this study is completely voluntary, which means that they can tell the study staff that they do not want to answer a question or complete a specific assessment if they do not want to. They will also be allowed to take breaks and will be offered refreshments during longer appointments. Participants are encouraged to break up assessments into multiple visits over 2-3 week periods to avoid fatigue and stress.

When training new assessors, the research staff trainees must sit in on appointments to observe the assessments and then go over scoring after the appointment is complete as the first stage of their training. Participants will always be asked if it is okay to have an additional person sit in on their visit for training purposes prior to the appointment session. If the participant agrees, then the trainee will be invited into the room.

The participant may choose to have a guest sit in on their appointments with them, if they would like. At the end of each appointment, particularly if sensitive questions are being asked (e.g., about sexual activity, drug use, etc.), the research staff may ask the guest to step out of the room to verify that there wasn't any further information that wasn't shared with the guest present.

Participants have the option to opt into un-encrypted emails from study staff to set up appointments or to discuss their study participation. Similarly, participants may opt into texting research staff on a University owned cell phone. If the participant does not give the study staff permission to contact via email or text, study staff will contact the participant by phone only. Participants will be able to indicate on their consent form which is their preferred method of contact: phone, email, or text. Participants may change their preferred method of contact at any point in the study, but if they have not already given permission for communication over email or text, they may be asked to sign an additional consent form for that mode of communication.

Additionally, participants will have the ability to opt into both texts and emails from the ClinCard service to receive updates on the payments sent to

the reloadable gift cards. If participants do not agree to receive texts or emails from the ClinCard program, they will receive communication directly from the study staff for when their cards have been refilled.

## 20.0 Compensation for Research-Related Injury

N/A

## 21.0 Consent Process

*21.1* Consent Process:

Consenting will take place in a private office at the University of Minnesota Department of Psychiatry, Ambulatory Research Center. Prior to the appointment, research staff will send copies of the consent form and HIPAA Authorization, as available, via email. Only the staff obtaining consent, the subject, and any family members or friends invited by the subject will be present. The participant may be asked if they are willing to have training research team staff sit in on the consent appointment to observe the consent process; however, the participant may decline to have this person the consent session. The research coordinator or other trained research staff will explain the study to the participant. After explaining the study, the participant 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, the participant can delay participation and return to sign the consent form at a later time. The participant will be allowed to review the consent form in private for as long as they need. The participant 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.

Documentation of consent, assessment of capacity to consent, and the HIPAA authorization will be captured digitally on REDCap using an iPad. Participants will be offered a physical copy of the consent form and HIPAA authorization to read through during the consent discussion, or they may follow along with the digital copy. After the UBACC assessment is completed (section 21.2), the research staff will bring the participant to the signature block on the consent page and provide instructions to electronically sign the consent form. The participant will then be instructed similarly on how to electronically sign the HIPAA authorization. If necessary,

study staff can capture consent using paper forms. If consent is captured on a paper form, the copies will be scanned into a dedicated folder on Box, and the original forms will be kept in a locked drawer in a locked office.

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 capacity to consent assessment 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.

In addition to the primary consent forms, we will have the subjects read and sign email communication and/or texting communication consent forms should they desire to opt into these types of communication. Participants currently enrolled in the study may also sign these consents at any time.

**COVID-19 Adaptations:** Due to the ongoing COVID-19 pandemic, the following modifications to study procedures may be used to mitigate pandemic-related risks while participating in this study.

- Consent procedures will be completed remotely through REDCap, while also using Zoom or a phone call to communicate. The consent form will be sent to the participant via email. Alternatively, study staff may be able to provide a web address and a survey code to open the consent survey.
- The electronic versions of forms in REDCap may be formatted slightly different than the paper versions, due to limited formatting options in REDCap.
- Participants will be prompted to enter a code during the consent procedures to ensure it is them completing the form. Study staff will provide the code through Zoom or by phone call.

*21.2* Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent:

To ensure that the potential participant has the capacity to provide informed consent, we will administer the UBACC prior to asking a participant to sign the consent documents. If the participant scores less than a 14 on the UBACC, the study staff obtaining consent may

review the study details in a single session of remedial education, and then administer the UBACC a second time. If the individual is still unable to score a 14 or higher on the UBACC after this remedial education, they will not be offered participation in the study. Individuals may be invited to participate at a later time if their cognitive status has improved in the opinion of their clinical care team and/or the PI. Participants who have had a medication change or hospitalization within one month of their consent appointment will be asked to wait to sign consent until they meet eligibility criteria. If participants sign consent before staff learn of medication changes or hospitalizations, they will be placed into a hold period until they are eligible to continue with baseline assessments.

At times when the clinical care team or the study staff believe that the participant's capacity to consent may have diminished, study staff may redo the consent discussion and re-administer the assessment of capacity to consent to determine if the participant is still able to consent to participate. If the participant is determined unable to participate at that time, the investigators will make a decision as to whether the participant will be placed on temporary hold or withdrawn from the study. If the participant is placed on hold, they must successfully complete the UBACC assessment again before continuing with study procedures.

Participants will not be invited for consent discussions during periods of greater impairment. Participants must have been in outpatient status for one month and on stable medications for one month prior to signing consent. If a participant is hospitalized for psychiatric reasons during the study, the PI will review the event and decide on a case-by-case basis if the participant should be withdrawn from the study. If the PI determines that the hospitalization is linked to study procedures or that continuing in the study could put the participant at greater risk, the participant will be withdrawn from the study treatment. Follow-up assessments may be completed on a case-by-case basis, as determined by the PI.

## 22.0 Setting

Research Sites: All research activities will take place in either the Department of Psychiatry Ambulatory Research Center or the Mental Health Neuromodulation Clinic in St. Louis Park. Remote study procedures may occur via Zoom teleconferencing or phone call.

Recruitment will occur at the UMP Psychiatry Outpatient Clinic, UMP Mental Health Neuromodulation Clinic, other partnered clinics within the community, and online.

## 23.0 Multi-Site Research

N/A

# 24.0 Resources Available

*24.1* Resources Available:

- Recruitment: We will be recruiting from the Psychiatry Clinic's Recruitment Registry, as well as contacting previous participants in our other research programs. Additionally, we will advertise locally within community settings.
- Facilities: We have three facilities that can accommodate research visits. The primary location is the Department of Psychiatry Ambulatory Research Center. There are four dedicated appointment rooms available to meet participants for study visits, as well as overflow space. In the Mental Health Neuromodulation Clinic in St. Louis Park, study staff are able to reserve private rooms to conduct study appointments as needed.
- Equipment: We have several iPads which can be used by research participants to complete their cognitive training during appointments. 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 via Ethernet. We have the necessary facilities to print subject binders. We have a StarStim tCS system..
- Emergency facilities: In the case that the participant has an emergency, such as a heart attack, or if they express suicidal intent during an interview, rescue resources will be made available to them. At the Department of Psychiatry Ambulatory Research Center, the Emergency Department is located one floor below. In the case of a health emergency, study staff can call in a code to have emergency personnel come to the scene. If a participant is expressing suicidal intentions or has behavioral problems that warrant hospitalization, the study staff may either escort them to the emergency department or can call for security. At the St. Louis Park location, medical staff are on hand in the case of a medical emergency. For medical and psychiatric emergencies, study staff will call 911 for the participant to be brought to a hospital.

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## 26.0 Appendix 1: Data Flow Diagram