PROTOCOL TITLE:

Minneapolis Community-Based Cognitive Training in Early Psychosis (Mini-COTES)

PRINCIPAL INVESTIGATOR or FACULTY ADVISOR:

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VERSION NUMBER/DATE:

Version 10.0 Date 21 April 9 2020

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
2.0	23OCT2017	● Added Faux Pas assessment ● Added C-SSRS to baseline ● Expanded the age range to include 16-35 year olds ● Added parental consent and minor assent ● Added optional video documentation of clinical interviews ● Corrected typos and errors in protocol and consent ● Updated inclusion/exclusion criteria ● Added EPIC calendar review as a potential recruitment tool at UMP Mental Health Neuromodulation clinic	Yes
3.0	24SEPT2018	● Updated inclusion/exclusion criteria ● Included REDCap digital consent, UBACC, HIPAA authorization as an option. ● Updated frequency of collecting Resource Utilization form ● Included digital option to collect Post Training Clinician Survey in REDCap. ● Substance Use Summary form previously used administered in intake demographics is now added to Post-Training and 6-Month Follow-Up assessments. ● Option to send a letter to the address of participants who have withdrawn and continue to possess lab materials.	
4.0	5OCT2018	● Updated UBACC passing criteria (75% correct needed to be included) ● Updated UBACC administration procedures for remedial education sessions	

		• Corrected error on UBACC form	
5.0	16 DEC 2018	• Added ability to text participants; added risk language to consent/assent forms; currently enrolled participants may sign an addendum consent form • Clarified language about email risks in consent/assent forms • Updated Neuropsych visit packets • Updated recruitment materials (new contact information) • Added addendum consent and assent forms • Added addendum UBACC	Yes
6.0	21 MAR 2019	• Clarified use of Skype and Facetime for remote clinical interviews • Clarified how addendum consents or assents will be used • Clarified data storage and management procedures • Added data flow diagram • Clarified that participants may choose to have only audio recordings instead of video • Added that participants who have their own device may use their own iPad to complete training if they wish; however, they will still be offered the use of a UMN iPad for their training. • Clarified that participants may be recruited from clinics that follow a NAVIGATE-like model, if the participant is treated for a psychotic illness with PI approval • Modified inclusion criteria so that participants that have a recent medication change may be enrolled and undergo intake assessments, and may proceed to baseline assessments with PI determination of non-significant	Yes

		modification to medication regimen ● Expanded window for appointments to allow for greater flexibility with participants; updated time estimates for appointments ● Updated title for Research Recruitment and Outreach Specialist. ● Indicated that MINI suicidality module is completed, just not used to determine suicidality risk ● Added a brochure to recruitment materials, updated flyer ● Reduced redundant language in protocols and consents ● Added information about data integrity and safety monitoring, compensation for research-related injury ● Added provision to allow staff to speak with family member or friend identified by participant ● Clarified waiver of consent for storing phone screens ● Added Release of Information for participants from non-UMP clinics ● Condensed and clarified consent form language	
7.0	24 MAY 2019	● Added unscheduled visits which can be used to complete assessments that weren't finished in previous appointments or in cases in which there were technical difficulties and data is missing ● Added payments for participants who wait during a scheduled appointment time, and study activities do not occur ● Added that diagnostic interviews may be video taped ● Specified that GPS tracking will be enabled on loaned iPads to allow	

		for remote wiping and locking using the "Find my iPad" feature ● Removed ProofPoint secure email as an option for communication; if participants would like to participate in optional email communication, they will be asked to sign the Unsecure Email Authorization Form. ● Updated intake packet ● Updated contact information on consent forms ● Removed references to redacting emails and texts – these data will be preserved in HIPAA compliant servers	
8.0	07 Jan 2020	● Removed the WRAT ● Removed asking participant's for permission to contact clinical providers to eliminate conflict with HIPAA Authorization ● Added that data may be shared between studies that share common assessments to reduce participant burden ● Clarified that participants who are committed to treatment during the study may still participate if the PI determines it is still in their best interest ● Clarified that participants returning from holds will have 4 weeks to complete study activities beginning on the date they re-enter the study ● Updated the REDCap data entry process ● Reduced redundant language ● Added Vinogradov Lab Data Safety Monitoring Plan ● Added Vinogradov Lab Crisis Protocol	Yes

		● Removed option to conduct interviews remotely	
		● Updated procedures for re-assessing capacity to consent in times of potential diminished capacity ● Updated procedures for participants who have been committed to treatment while participating in the study	
9.0	06 April 2020	● COVID19 update ● Added the ability to conduct study procedures remotely via Zoom or phone call ● Extended the assessment windows to allow for greater flexibility in conducting assessments ● Extended the length of time to complete training ● Improved communication options for potential participants who expressed interest but are not yet enrolled ● Added COPRR database as a recruitment and data sharing platform ● Reduction of redundant language and restructuring of some sections for increased clarity	Yes
10.0	21 April 2020	● Added COVID19 questionnaire ● Increased flexibility of appointment schedules during COVID19 social distancing requirements	No

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ABBREVIATIONS/DEFINITIONS

- BIS/BAS: Behavioral Inhibition System/Behavioral Activation System
- BVMT: Brief Visuospatial Memory Test
- CAINS: Clinical Assessment Interview for Negative Systems
- COTES: Community-Based Cognitive Training in Early Psychosis
- CPT-IP: Continuous Performance test—Identical Pairs
- CPZ: chlorpromazine, an antipsychotic
- C-SSRS: Columbia Suicide Severity Rating Scale
- FEPP: First Episode Psychosis Program
- GAF: Global Assessment of Functioning
- GCE: Generalized Cognitive Exercises
- HCMC: Hennepin County Medical Center
- HVLT: Hopkins Verbal Learning Test
- ISMI: Internalized Stigma of Mental Illness
- MCCB: MATRICS Consensus Cognitive Battery
- MEG: Magneto-Encephalography
- MINI: Mini International Neuropsychiatric Interview
- MSCEIT: Mayer-Salovey-Caruso Emotional Intelligence
- NAB: Neuropsychological Assessment Battery
- PANSS: Positive and Negative Syndrome Scale
- PROID: Penn Prosody Identification
- QLS: Quality of Life Scale
- RMET: Reading the Mind in the Eyes
- SCID: Structured Clinical Interview for DSM-5
- SFS: Social Functioning Scale
- TAU: Treatment as Usual
- TCT: Targeted Cognitive Training
- TEPS: Temporal Experience of Pleasure Scale
- UMP: University of Minnesota Physicians
- UPSA-B: UCSD Performance Based Skills Assessment
- WMS: Wechsler Memory Span
- WTAR: Wechsler Test of Adult Reading

STUDY SUMMARY

Study Title	Minnesota Community-Based Cognitive Training in Early Psychosis (Mini-COTES)
Study Design	Randomized controlled trial comparing 2 interventions against one control condition
Primary Objective	Perform a double-blind RCT of web-based, portable computerized cognitive training in young individuals with recent onset psychosis receiving treatment within the University of Minnesota, Department of Psychiatry's First Episode Psychosis Program or other state clinics utilizing the NAVIGATE treatment model.
Secondary Objective(s)	1. Compare the clinical and cognitive effects of neural system-informed TCT that focuses explicitly and specifically on distributed neural system efficiency in auditory/verbal and social cognitive domains, vs. more non-specific GCE designed to enhance executive functioning and problem-solving, vs. TAU. Determine the durability of these effects and their relationship to functional outcome over a 6 month period. 2. As a secondary aim, investigate the feasibility, tolerability, and acceptability of the intervention by service providers, clients, and caregivers in these real-world treatment centers.
Primary Study Intervention or Interaction	Cognitive training exercises produced by Posit Science
Study Population	First Episode Psychosis patients aged 16-35
Sample Size (number of participants)	235 (150 to provide complete data)
Study Duration for Individual Participants	8-15 months

1.0 Objectives

1.1 Purpose: The purpose of this study is to determine whether cognitive training might help people with recent-onset psychosis lessen their symptoms and learn new thinking and problem-solving skills, when it is delivered on iPads and integrated into an early psychosis treatment program. We will determine whether any observed changes in symptoms, cognition, and functional status are due to the cognitive training or are the result of early intervention treatment within the First Episode Psychosis Program (FEPP) or a clinic following the NAVIGATE model. Additionally, we will determine whether there is a difference in cognitive gains between participants who complete a targeted computer training program with auditory and social cognition components and those who participate in a general cognitive training program designed to treat executive functioning.

2.0 Background

2.1 Significance of Research Question/Purpose: New longitudinal data indicate that current early intervention programs may not significantly alter long-term outcome, suggesting that a critical treatment target yet remains unaddressed. We propose that cognition is such a critical target and that it must be addressed vigorously as soon as a young individual with recent onset of psychosis enters clinical care. The development of effective treatment to improve cognition early in the course of schizophrenia has a strong likelihood of significantly altering long-term community outcomes (9).

Emerging evidence on the serious metabolic and perhaps neurologic side effects of antipsychotic medications make it imperative for us to develop additional efficacious treatments that do not compromise the health and well-being of our young patients (10). Cognitive training appears to be an intervention without unwanted deleterious effects on either metabolism or neural substrates. Indeed, our data in adults with persistent schizophrenia suggests that it may have “neuro-restorative” or neurotrophic effects (11,12).

Current controversy exists in the field on the relative merits of various cognitive training approaches. It is nearly impossible to compare results across studies due to wide variations in treatment design, sample sized, use of blinds, nature of control conditions, and use of adjunctive interventions. Establishing the relative effectiveness of TCT vs. GCE within one single, appropriately powered, double-blind study will provide important data for the field for the development and delivery of future cognitive training interventions.

One of the greatest barriers to having an impact on public health in the area of serious mental illness is the lack of translational research examining the effectiveness of novel interventions in real-world treatment settings. The proposed study goes beyond a typical efficacy study of cognitive training to examine the feasibility of offering this intervention in real-world settings that treatment patients on the "front lines" of community mental health services.

Young individuals with schizophrenia are sensate to the stigma of needing to engage in mental health care. Treatments that require frequent clinic visits are at odds with a recovery orientation that encourages return to work, school, and social engagements. A scalable behavioral intervention on a portable device may be potentially free of stigma, and may revolutionize our psychiatric armamentarium for young people.

2.2 Purpose and Background: Our field recognizes the imperative need for early detection and pre-emptive interventions in serious illnesses such as schizophrenia (16, 17). The RAISE initiative is investigating integrated multi-modal treatment with the goal of reducing symptoms and enhancing community functioning, but as of yet, there are no systematic, scientifically-informed, scalable approaches to targeting and pre-empting what is arguably a core biological vulnerability factor in early schizophrenia: cognitive dysfunction.

Cognitive dysfunction represents a significant risk factor for schizophrenia and a poor prognostic indicator. Relative to normative samples, high risk individuals show deficits in IQ, vigilance, speed of processing, working memory, verbal learning and memory, executive functioning, global cognition, and social cognition prior to the first psychotic episode (18,19,20,21,22). From high risk status to first psychotic episode, individuals show continued cognitive impairment (18, 23), or further cognitive decline (20, 21, 24, 25). At first psychotic episode, multiple cognitive deficits are evident, with the largest impairments seen in processing speed and immediate verbal memory (26). Importantly, verbal memory, processing speed, and attention at first episode predict community functioning seven years later (2).

Neuroimaging studies reveal that early psychotic illness is characterized by progressive brain volumetric changes, abnormal/inefficient neural network activation, and functional disconnectivity across frontal and temporal cortical regions (27,28,29,30,31). Early schizophrenia can thus be conceptualized as the initial expression of a developmentally-based neurocognitive disorder that is characterized by inefficient and poorly integrated cortical processing. Cognitive dysfunction and underlying neural network inefficiency—especially across fronto-temporal systems—should

therefore be one of the primary targets for early intervention. The need for effective cognitive interventions delivered early in the course of illness is critical given that, to date, cognitive-enhancing pharmacological agents have proven disappointing (32) and given emerging findings about the potential deleterious long-term neural effects of antipsychotic medications (10).

Meta-analytic work confirms that a wide range of non-computerized and computerized approaches results in moderate increases in global cognition measures in patients with chronic schizophrenia (8,33). However, only 4 studies to date have reported the effects in individuals at clinical high risk (34,35) or in recent onset patients (13,36,37,38,39).

Rauchensteiner et al. (35) compared the effects of computerized training in individuals at risk for psychosis versus those with chronic schizophrenia and found significantly greater gains in verbal memory in the high-risk group. Younger subjects also showed meaningful gains after only 10 sessions of training, but those with chronic schizophrenia did not. These differential responses to a relatively brief course of training suggest that a meaningful treatment response may be obtained with a more efficient intervention if we capitalize on the greater neuroplastic capacity in young individuals.

Bechdolf et al. (34) tested the effects of an integrated psychological intervention (IPI) which included 12 sessions of computerized cognitive training, relative to supportive counseling in individuals in an early initial prodromal state. Subjects in IPI showed a significantly lower rate of conversion to psychosis up to 12 months after treatment. While these results are encouraging, the trial design did not allow assessment of the relative contribution of computerized cognitive training to this outcome and the effects on cognitive performance were not reported. Additionally, the majority of high-risk patients will not develop full psychosis, even without intervention, and they tend to have less severe cognitive deficits than those seen in full-blown schizophrenia. Whether these effects can be achieved after illness onset but early in the course of the disorder is still unknown.

Eack et al. (13) examined cognitive enhancement therapy (CET) in recent onset schizophrenia versus enriched supportive therapy (EST) delivered over 2 years. Moderate improvements in cognition were seen only after 2 years. CET subjects also showed significant gains on social cognition, social adjustment, and symptoms, and a significantly greater proportion of them were engaged in competitive employment at 2 years. Further, the gains in cognition from baseline to two years of treatment were significantly associated with gains in functional outcome (37). .Eack et al (38) also found greater preservation of gray matter volume over 2 years in the left

hippocampus, parahippocampal gyrus, and fusiform gyrus, and significantly greater gray matter increases in the left amygdala in CET subjects relative to EST subjects.

Finally, our group recently completed a double-blind RCT on the effects of TCT versus an active control condition of computer games (CG) in 80 subjects with recent onset schizophrenia, delivered as a stand-alone treatment via laptops in conjunction with usual care in two university-based specialized clinics. Briefly, subjects in the TCT condition showed significant gains in global cognition, verbal learning and memory, and problem solving compared to the CG group.

While cognitive training shows a high degree of promise, we have argued that it must be developed using systems neuroscience rationale, and that it must be designed to deliver highly targeted and well-defined interventions to impaired neural systems in order to generate the most robust and reliable therapeutic gains possible for patients (7). However, these ideas are controversial and at a recent NIMH-sponsored workshop, several senior investigators in the field argued that a range of different general cognitive remediation approaches have a sufficiently strong evidence-base is in fact rather weak, and that the modest behavioral improvements seen after a wide variety of interventions represent the effects of general cognitive stimulation rather than specific distributed neural system improvements which will result in reliable and enduring gains (7). In this proposal, we put this assumption to the direct test. First, we note the following findings from 5 double-blind RCTs performed in this field:

1. In a small inpatient study, Popov et al (14, 15) found a more robust cognitive effect from TCT vs GCR as well as more meaningful improvements in MEG measures of neural system dysfunction. Keefe et al. (41) found significant between-group difference after 20 hours of TCT vs. computer games in a small feasibility study with chronically ill outpatients.
2. Our imaging data indicates that TCT drives specific improvements in auditory system operations as well as transfer to untrained working memory and problem-solving functions (12, 42). Improvements in prefrontal cortical activation patterns after TCT correlate with better functional outcome measures at 6 months. In contrast, prefrontal and behavioral gains seen in a computer games control group show no correlation with outcome measures at 6 months, suggesting that the games do initially provide some prefrontal stimulation, but do not result in enduring neural system adaptations associated with better functioning.

3. In one of the few rigorous double-blind RCTs with chronically ill outpatients, Dickinson et al. (43) found no significant group differences between a cognitive remediation program based on problem-solving educational software vs. game-based software.

Taken together, these findings indicate that a targeted approach to training specific impairments in neural system functioning can drive improvements in those neural systems, and that these improvements show a correlation with better real-world functioning at 6 month follow-up. In contrast, more general cognitive stimulation as offered by a range of activities, including problem-solving exercises, may enhance prefrontal activation and even induce some non-specific improvements in behavioral performance over the short-term, but without driving specific improvements in key distributed neural systems, and without any clear association to real-world functional gains at 6 month follow-up in the absence of a psycho-social treatment "wrapper."

Two meta-analyses of cognitive training RCTs in schizophrenia (8,33) found larger effect sized for improvements in social and role functioning when cognitive training was combined with psychiatric rehabilitation approaches (d=0.47 and 0.59) than when administered alone (d = 0.05 and 0.28). Another emerging area is the growing activity and involvement of consumers, caregivers, and other stakeholders in the recovery movement and treatment development process in their community settings. For this reason, the proposed study will take place in specialized early intervention programs within the community that offer a range of psychosocial supports to participants, and will actively empower caregivers, participants, and clinicians to give us ongoing feedback about the intervention.

3.0 Study Specific Aims

3.1 Specific Aims:

1. Perform a double-blind RCT of web-based, portable computerized cognitive training in young individuals with recent onset psychosis receiving treatment within the University of Minnesota, Department of Psychiatry's First Episode Psychosis Program or other state clinics utilizing the NAVIGATE treatment model.

2. Compare the clinical and cognitive effects of neural system-informed TCT that focuses explicitly and specifically on distributed neural system efficiency in auditory/verbal and social cognitive domains, vs. more non-specific GCE designed to enhance executive functioning and problem-solving, vs. TAU. Determine the durability of these effects and their relationship to functional outcome over a 6 month period.

3. As a secondary aim, investigate the feasibility, tolerability, and acceptability of the intervention by service providers, clients, and caregivers in these real-world treatment centers.

3.2 Hypotheses to be tested:

1. TCT participants will show significantly greater gains in general cognition, verbal learning/memory, and social cognition compared to GCE and TAU participants. These gains in the TCT group will be sustained at 6-month follow-up.
2. GCE participants will show improvement in problem-solving and global cognition compared to TAU participants. At 6 month follow-up, GCE participants will show lower gains in global cognition and verbal learning/memory than TCT participants.
3. Gains in general cognition and processing speed, and in social cognition in TCT participants will correlate with improvements on 6-month measures of occupational and social functioning, respectively, as well as internalized stigma. These associations will be significantly greater in TCT participants vs. GCE or TAU participants.
4. Symptom ratings will show improvement in all participant groups at 6 months, with no significant between-group differences.
5. At least 70% of randomized clients will complete >20 hours of training in the TCT and GCE arms.
6. Participants and clinicians will rate the TCT and GCE interventions as equally feasible, tolerable, and acceptable.

4.0 Study Intervention(s)/Interaction(s)

4.1 Intervention: This protocol examines the effects of two modes of remote cognitive training compared to regular clinical care over a period of 6-12 weeks. Participants will be randomized to one of three conditions: Targeted Cognitive Training, General Cognitive Exercises, or Treatment as Usual.

Participants randomized to one of the two training conditions will be asked to complete 60 minutes of training 5 times per week over the course of 6 weeks for a total of 30 hours of training. They will be loaned an iPad to complete their training sessions remotely at home, or they may come to the Department of Psychiatry to complete their training. Participants who have their own device may use their own iPad to complete training if they wish; however, they will still be offered the use of a UMN iPad for their training. Though we will encourage participants to complete

the training within a 6 week period, we will allow them up to 12 weeks to complete the training protocol.

Participants randomized to the treatment as usual condition will continue receiving their standard care from the First Episode Psychosis Program or a clinic utilizing the NAVIGATE model. After they complete their final assessment, participants in the treatment as usual group will be offered access to the training program of their choice, if they would like to complete the training.

Assessments will be conducted at Baseline, End of Intervention/12 weeks, and after a 6 month follow up to determine the effects of training on symptoms, behaviors, cognition, and social cognition.

4.2 Targeted Cognitive Training (TCT): The TCT program will be provided by Posit Science free of charge and will consist of a set of iPad application-based exercises in two components: an auditory/verbal processing training module which will be applied for 20 hours, and a social cognition training module which will be applied for 10 hours. Compliance is monitored by data upload following each training session.

- Auditory Training Module (20 hours): This suite of exercises has been extensively studied by us and has been described in detail in Fisher et al. (44). In brief, the auditory program consists of a set of computerized exercises designed to improve the speed and accuracy of auditory information processing while engaging working memory and cognitive control under conditions of close attention and reward. The rationale is to train the brain to generate precise and reliable neurological responses to the frequency, timing, and complex sequential relationships between speech sounds. Exercises continuously adjust difficulty level to user performance to maintain an approximately 80% correct performance rate. Correct trials are rewarded with points and animations. Exercises contain stimulus sets spanning the acoustic organization of speech. During the initial stages of training, auditory stimuli are processed to exaggerate the rapid temporal transitions within the stimuli by increasing their amplitude and stretching them in time. The goal of the processing is to increase the effectiveness by which these stimuli engage and drive plastic changes in brain auditory systems that in an individual with schizophrenia exhibit relatively poor temporal response. This exaggeration is gradually removed so that by the end of training, all auditory stimuli have temporal characteristics representative of real-world rapid speech.
- Social Cognition Training Module (10 hours): This training module consists of 7 iPad application-based exercises designed to ameliorate core deficits in social cognition expressed in schizophrenia and in

children diagnosed with Autistic Spectrum Disorders (ASD). The exercises apply principles of implicit learning to restore the brain's capacity to process and utilize socially-relevant information, and includes training to improve affect perception (both visual and vocal), social cue perception (in faces, gazes, social situations), theory of mind, self-referential style, and emotion labeling and working memory. The exercises are embedded in a user-friendly, easy-to-use game wrapper in which learners can track their performance and progressions, and earn game points and friends. Preliminary data show good initial feasibility of the exercises in ASD participants, as well as efficacy in driving neurological and behavioral improvements in schizophrenia patients.

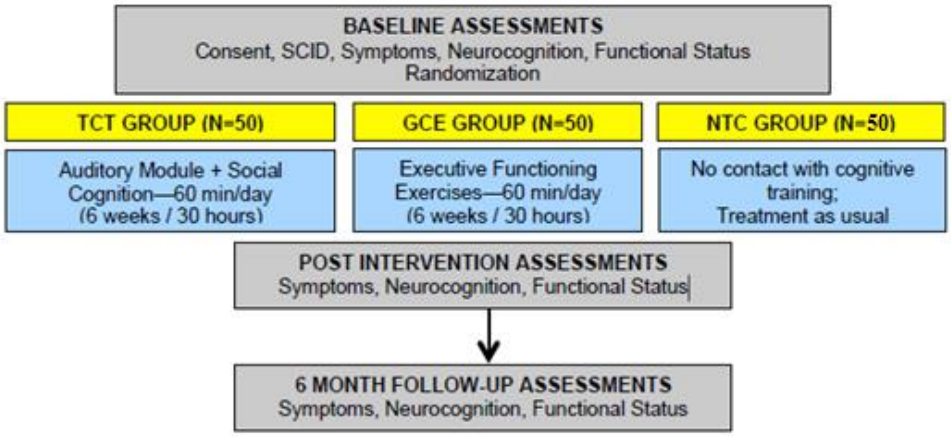
4.3 General Cognitive Exercises (GCE): An alternative view to cognitive training in schizophrenia posits that there is little difference among the various approaches and that what is important is the explicit reinforcement of strategies that teach participants to apply cognitive gains to real life (8). We will test this prediction by contrasting TCT with a set of general cognitive exercises (GCE) that also provide engaging, adaptive training as described above; both approaches will be embedded in the same early intervention NAVIGATE support model, but no explicit transfer strategies will be taught to any participants. The GCE will focus on executive dysfunction, as this domain is a significant, functionally important area of deficit in schizophrenia and has been the target of many previous studies (52, 53). We will train this domain using a suite of engaging, adaptive web-based exercises that target executive function, intelligence, and spatial navigation developed by Posit Science.

4.4 Treatment as Usual (TAU): We will assess 50 participants who receive early intervention services through the NAVIGATE clinic alone (with no cognitive training) in order to determine: 1) whether any observed changes in symptoms, cognition, and functional status are the result of the cognitive training or are the result of FEPP treatment; 2) whether recent onset participants who receive NAVIGATE clinic services but no cognitive training show a decrease in cognition over the course of the study. In our previous study, recent onset patients who completed a computer games control condition showed a decline in verbal learning and memory at trend level after the 8 weeks of intervention. However, we were unable to determine whether this was a spurious finding, the result of illness progression in these young individuals, or the effects of intensive visuo-spatial processing from 40 hours of computer games resulting in competitive interference during the verbal memory task. With the use of a no-training control group in this study design, we will be able to assess any cognitive and functional changes observed in the TCT and GCE groups against the "normal" trajectory of cognitive change that is observed in a recent-onset group who receives specialized early intervention services treatment but no intervention targeting cognition.

Participants who are randomized to this arm of the study will be offered access to the program of their choice after the completion of their 6 month follow up visit.

5.0 Procedures Involved

5.1 Study Design: This is a double-blind, RCT performed in the University of Minnesota Department of Psychiatry. 235 participants (150 expected to provide complete data) with recent-onset psychosis will be stratified by education and symptom severity and will be randomized into one of three intervention groups: 1) Web-based targeted cognitive training (TCT); 2) Web-based general cognitive exercises focusing on executive dysfunction (GCE); or 3) treatment as usual (TAU). All participants will be asked to participate in a screening/baseline battery ; a 12 week Intervention Phase where they receive computerized training or treatment as usual; a post-intervention follow up assessment battery ; and a 6 month follow-up assessment battery . Total participation will last approximately 36-52 weeks (9-12 months).



5.2 Study Procedures:

For a graphical representation of study procedures, please refer to Section 26 Schedule of Events. Section 6.2 Data contains a full list of the assessments and measures collected in this study.

At any point in the study, unscheduled visits may be used to collect data that was missed during previous appointments (e.g., a visit was cut short; technical difficulties prevented data collection).

For all study timepoints, a limited battery may be delivered remotely; these items have been identified in Section 6.2 Data and Section 25 Schedule of Events. Interviews and cognitive measures will be conducted over Zoom teleconferencing

or by phone, and self-report assessments may be completed via links to a REDCap database sent over email.

Pre-Screening: Potential participants will be provided with information about the study using an established script and will be asked a series of questions to determine if they meet basic inclusion/exclusion criteria. They will be told about the basic aims of the study. Individuals who are interested in participating and appear to qualify for the study will be invited to a consent discussion (see Section 22 Consent Procedures).

Screening/Baseline Assessments (1-4 weeks): After the participant has provided informed consent, we will begin conducting the screening assessments to determine their eligibility to participate in the study. Eligibility to participate will be determined through use of the MINI and/or a review of recent medical history, including medications. Participants may complete intake interviews while waiting to achieve clinical stability in medication regimen (recent changes to medication are permissible). The suicidality module of the MINI will not be used to assess suicidality risk; instead, the C-SSRS will be used at screening to determine past behavior and current risk. If a C-SSRS is not conclusive towards the suicidality risk of a participant, study staff may consult with the participant's clinician to determine whether they are clinically stable enough to participate in the study. This determination will be documented as a Note to File within the participant's record. A SCID may be conducted in more complex cases where a MINI does not deliver a clear diagnosis. Other eligibility assessments include the demographics, WTAR, and Substance Use Summary forms. If the participant qualifies to participate in the study, Baseline evaluations will begin.

Participants must be clinically stable before beginning baseline assessments, defined as no hospitalizations or significant changes to medication regimens for a minimum 30 days. The PI will make case by case determinations as to whether a change in medication constitutes a significant change. Baseline assessments will evaluate neurocognition, social cognition, clinical symptoms, and functional status, as well as computer, video game and internet usage. For a list of the assessments used, please refer to Section 6.2 Data and Section 26 Schedule of Events.

Total baseline assessment time for neurocognition, clinical symptoms, functional status, and user ratings will be approximately 7 hours spread over 1-4 appointments in a 1-4 week period. Participants who are placed on a hold due to medication changes or hospitalizations will have 1 to 4 weeks to complete the baseline assessments once they re-enter the study.

If participants provide their consent for the interviews to be videotaped or audio recorded, a video camera will be set up to record the participant during their diagnostic and/or clinical interview. For in person visits, a camera will be

positioned so the participant's face and body are visible to capture affective changes and motor behaviors. If the participant only provides permission for audio recording, the camera will still record, but the viewfinder will be closed. Interviews will not be recorded during remote visits. Please refer to Section 6.0 Data Banking for clarification on how video data will be stored.

After baseline measurements have been completed, the participant will be randomized to one of the three study arms.

Intervention Phase (6-12 weeks): For participants who are randomized to TCT or GCE, we will ask them to complete 60 minutes of training 5 times a week (5 hours per week) over the course of 6 weeks for a total of 30 hours of training. Though we will encourage participants to complete the training within a 6 week period, we will allow them up to 12 weeks to complete the training protocol. IPads loaned to participants may be delivered via the mail. Prior to mailing, staff will follow the manufacture's guidelines to disinfect the iPads using a 70 percent isopropyl alcohol wipe or Clorox Disinfecting Wipes. Study participants randomized to the cognitive training conditions will maintain weekly contact with study staff by telephone, text, and/or email to check in on their training progress, to see if they have had any adverse events, and to ensure that they wish to remain in the study.

Study participants who are randomized to TAU will not be regularly contacted by study staff until it is time to schedule their Post-Intervention Assessments (12 weeks post Baseline). Participants will be asked to contact study staff if they have any adverse events, such as hospitalization; however, this will be reviewed when scheduling the participant for their next visit. Study staff may contact participants during the 12 week period as needed to inform them of changes to the project or to keep them engaged in the study.

For a description of the training programs, please refer to Section 4.

Post-Intervention Assessments (1-4 weeks): After the participants have completed the Intervention Phase, they will be invited to participate in post-intervention assessments. Their appointments will be scheduled after completing the training program, notifying study staff that they no longer wish to participate in training, or after 12 weeks have passed since the Baseline Assessments were completed. The Post-Intervention Assessments should last approximately 5 hours and may be split up into 1-4 visits across 1-4 weeks. We will repeat the baseline measurements in neurocognition, social cognition, clinical symptoms, and functional status, as well as Resource Utilization and Substance Use summary forms. If participants have consented to audio or video recording, their clinical interview will be recorded following the procedures described above.

In addition to repeating baseline measures, we will measure the feasibility and acceptability of the cognitive training programs through 1) attrition rates; 2) time to completion of training; 3) user and clinician ratings of acceptability.

Participants who completed training will be asked to complete a 22-item, Likert-type questionnaire composed of elements of a measure used previously by Posit Science to evaluate acceptability for their cognitive training software, and components of a measure we have used previously to assess acceptability of training in our recent-onset RCT. Items assess user experience and satisfaction with the programs, the web-based administration, and the training schedule. We will also collect this data from their treating clinician in the First Episode Psychosis clinic. These questionnaires may be completed in-person or collected remotely using REDCap. For participants who are lost to follow up and are unable to provide this data, study staff will complete the Participant Closeout Report to provide some final data on their participation in their case records.

If participants were loaned an iPad and/or other devices to complete study activities at home and no longer wish to participate in study activities, including their post-intervention interviews, study staff will attempt to coordinate with the participant to meet them before or after a regularly scheduled clinic appointment to return the device(s). If the participant is no longer receiving care at the UMP Psychiatry Clinics, if in-person appointments are not available, or if they cannot be reached, study staff will send them a letter asking them to return the devices along with a box with a return label. Participants will be invited to come back for their post-intervention visit in this letter, but also reminded that they are free to no longer participate in the study.

6 Month Follow-Up: Participants will enter the follow up period after the completion of their Post-Intervention Assessments. We will ask them to refrain from participating in any other research studies or completing other commercially available cognitive training programs during this time to avoid confounding our results. We will inform them that if they wish to participate in another study or complete a different cognitive training program they may do so, but we would withdraw them from this study at that time.

Study staff may contact participants during the six-month follow up period as needed to inform them of changes to the project or to keep them engaged in the research. Participants will be contacted 2-4 weeks before their approximate 6 month follow-up date to verify that they wish to continue participating and to schedule their appointment. We will repeat the baseline measurements in neurocognition, social cognition, clinical symptoms, and functional status, as well

as Resource Utilization and Substance Use Summary forms. If participants have consented to audio or video recording, their clinical interview will be recorded following the procedures described above. The batteries should last approximately 5 hours and may be split up into 1-4 visits across 1-4 weeks. Upon completion, the participant will have completed the study. Participants who were randomized to the TAU arm will now be offered access to either of the computerized training programs.

COVID19 Procedures

Due to social distancing requirements during the COVID19 outbreak, participants will not be able to attend in-person visits. To accommodate for this situation, participants will be asked to complete remote assessments using a limited battery, which is identified in Section 6.2 Data and Section 26 Schedule of Events. Any missing data from in-person assessments may be collected later once social distancing procedures are lifted, at PI discretion.
To further accommodate participants' needs, the timeframes during which study activities can be completed will be extended while social distancing procedures are in place. These accommodations will be temporary; when social distancing procedures are lifted, study timeframes will return to the windows described above. At this time, the PI will make case-by-case determinations as to whether participants will be expected to adhere to the standard timeframes or the COVID19 timeframes for their current event window.

The adjusted timeframes are as follows:
- Screening/Baseline: 1-6 weeks
- Intervention Period: 6-16 weeks
- Post-Intervention Assessment: 1-6 weeks
- 6 Month Follow-Up Assessment: 1-6 weeks
- Total duration of study activities: 35-60 weeks (8-15 months)

However, if participants need additional time due to illness, caring for loved ones who are ill, or other extenuating circumstances related to COVID19, they will be provided additional support and time to complete the assessment battery, at PI discretion.

5.3 Individually Identifiable Health Information:

Participation in this study will involve collection of individually identifiable information. This includes:

- Full name
- Contact information: Phone number, email address, mailing address
- Date of Birth

- Medical Record Number
- Study staff may review the participant's Electronic Medical Record (EMR) to confirm appointment scheduling, medication lists, diagnostic information, and for review of treatment services utilized during the study. In the case of significant medical events (e.g., traumatic brain injury), study staff may review the EMR or request records from their treating clinicians to provide context for study data.
- If a participant is going to earn over $600 in a calendar year for study compensation, we will require the participant's Social Security Number to report their earnings to the IRS.
- Participants will be asked to provide consent for videotaping or audio recording of their clinical assessments

For further details about the storage of PHI, please refer to the following sections: 6.0 Data Banking; 12.5 Payment; 17.0 Data Management; 20.0 Provisions to Protect the Privacy Interests of Participants.

6.0 Data Banking

6.1 Storage and Access:

All data management servers will meet all relevant privacy and security standards for electronic clinical trial data entry and 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 the authority to review study records. Identifying information will not be shared outside of the UMN study team and its collaborators (the University of California San Francisco, Posit Science Corporation, and the University of Pennsylvania) 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 UBACC, HIPAA Authorizations, and communication authorizations, will be collected and stored in UMN REDCap. If need be, participants may still complete paper consent documents. Copies of physical consents will be uploaded into a dedicated folder within Box, while the originals will remain in locked cabinets in locked offices. The consents will be separated from the participant binders to keep participant PHI separated from study data. 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. Consent documents will not be shared outside of the UMN study team unless required by law.

If a participant has requested to receive a copy of their signed consent forms over email, study staff may temporarily download the consent documents from REDCap or Box to their AHC-IS computer in order to attach the file to an email.

Assessment and Training data:

The majority of the assessment data will be collected on paper forms, which will be kept in individual binders for each participant. These binders will be stored in locked cabinets in locked offices. Certain self-report assessments may be collected and stored in UMN REDCap.

For visits conducted remotely or if binders are inaccessible, study staff may temporarily download digital versions of these assessment forms to their ACH-IS computer in order to take notes. Once complete, staff will upload the digital files to the participant's folder on Box. Scores may later be recorded in a participant's binder to facilitate first and second scoring. Additionally, several assessments include participant-facing documents that are normally handed to participants during in-person appointments. Study staff will email participants a PDF copy of these documents for their reference during remote visits.

Some activities will involve computerized programs. All assessments or scoring of assessment data will involve AHC-IS managed computers. The study team will loan AHC-IS managed iPads to some participants in order to complete their BrainHQ cognitive training at home. Study staff will wipe the iPad when it is returned to the lab to remove any previous data (i.e., Wifi log in information) that may have been stored on the device.

Several assessments will involve MCCB software that is installed on lab computers. The CPT-IP assessment will be conducted on an assessment laptop. The results will be printed off and stored in the participant's binder. The MSCEIT 4 software (part of the MCCB software package) will be used to

grade the MSCEIT assessment.The MCCB T-scores will be generated with the MCCB scoring program. An Excel Spreadsheet will be used to calculate the standardized scores for the Faux Pas and Social Functioning Scale assessments; these data will not contain PHI and will not be saved. Study staff will take outcome scores from the participant's binder and enter it into the programs to obtain standardized scores, which will be recorded on the participant's summary score sheet in their binder. The outcome scores for the CPT-IP, MCCB, and the MSCEIT will be saved to the computer but will not contain any PHI; all data is stored underneath the participant's ID and visit code. Study team members will regularly delete the data from the computers after the data has been entered into the participant's binder and the REDCap database.

Performance data for the Penn CNB will be collected through the University of Pennsylvania Penn CNB portal and will be stored on University of Pennsylvania secure servers. The data collected will not contain any direct identifiers; instead, the data will be associated with the participant's unique study ID. However, study staff will enter the participant's date of birth into the web portal to confirm the participant's age at time of assessment. Participants are given a coded identifier at the beginning of a testing session by a researcher and no other identifiable information is required to begin a testing session and collect data on the Penn CNB. The data will be exported from University of Pennsylvania servers to Box at interim and final analyses and merged with the master data set. This data will remain on University of Pennsylvania servers and on Box indefinitely.

Performance data from BrainHQ cognitive assessments will be collected on the BrainHQ web portal. Data collected during remote cognitive training will be collected through the BrainHQ iOS app. All BrainHQ data will be stored on secure servers hosted by Posit Science Corporation; no data will be stored locally on devices running the BrainHQ software. Study staff will create an account for the participant to complete their training and their cognitive assessments. Direct identifiers will not be shared with Posit Science. A BAA exists between Posit Science and the University of Minnesota Department of Psychiatry to allow sharing of participant data. Posit Science will maintain records of all data generated in this study to use for their own purposes indefinitely. Study staff will extract the assessment data from the BrainHQ website and store this data in Box for further analysis. Please refer to section 18.0 Confidentiality for information about the de-identification of data.

Data from this study will be entered into the University of Minnesota Mini-COTES REDCap database. As this study is being conducted in partnership with the COTES protocol at UCSF (see study "Community-Based Cognitive Training in Early Schizophrenia," 1607S90201), this database will later be

merged with the University of California San Francisco COTES REDCap database for permanent storage. At the end of the study, the UCSF REDCap data will be extracted to UMN Box for further analysis. This data will contain some PHI in the form of date of birth and date of data collection, but will not contain participant names or contact information. The study team has a DUA with UCSF to allow for the sharing of this data between institutions.

Video or Audio Data:

Video/audio data will be recorded with a camcorder using an SD card. After the assessment appointment is complete, a member of the study staff will upload the file into a secure folder within Box. If the study staff is not able to immediately upload the video/audio file onto Box, the device will be stored in a locked cabinet in a locked office until the upload can be completed. Once the study staff has confirmed that the file has successfully uploaded to Box the video/audio file will be erased from the device. In the case that a video/audio file needs to be downloaded off of Box for viewing it will be stored on an AHC-IS supported computer. The audio/video data will be deleted from the computer after viewing is complete. However, this option will only be used if absolutely necessary; whenever possible, all viewing will take place within the Box server. Access to the folders will be shared with qualified study staff and collaborators on a per-need basis, and only qualified study staff listed on the delegation of authority log will have access beyond Viewer level. Study staff will regularly check who has permissions to the video/audio folder and will remove users who no longer need access to the files. Video/audio data will be stored indefinitely if the participants agreed to have their video/audio data used for other research purposes or for training purposes. If participants did not consent to these uses of their video/audio data, the files will be erased when data analysis for this project is complete.

Other Study Data:

Participants will be asked during their consent form whether they would like to be contacted in the future for additional opportunities to participate in research. Should they agree to do so, their name, contact information, and relevant demographic information such as age, gender, and/or diagnosis will be added to a potential participant registry. This information will be maintained in Box by the study team, and may be disclosed to collaborators with IRB-approved studies. This information will be disclosed to participants in the consent form.

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 study ID numbers and personal identifiers, including alternate IDs (e.g., Posit Science). These records will be maintained for a minimum of six years after completion of the study.

If a participant has consented to text messaging, 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. When the cell phone is not in use, it will be stored securely (e.g., in a locked cabinet in a locked office). Primarily the phone will be stored at the Department of Psychiatry. However, staff may take the phone with them during certain circumstances, such as: travelling between research sites; in preparation for weekend appointments; and when working from home. 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.

Emails that participants send to study staff will not be deleted and will be maintained as part of the study record, until documents containing PHI for the study are deleted. If the emails include significant information relevant to the participant's health or study status, they will be maintained indefinitely as part of the study record. Access to the study email account will be limited to members of the study team who coordinate appointments with study staff, though access can be provided as required for institutional review.

In order to be reimbursed for parking, participants must email or text a picture of the parking receipt to staff, or bring the receipt to staff at their next appointment. For audit purposes, staff will save these pictures to a dedicated folder on Box.

If a potential participant does not qualify for the study based on the phone screen, study staff will ask if they would like to be contacted for other research opportunities in the future. If the individual agrees, the study staff will gain verbal permission to store their phone screen and add their

contact information to a research registry. The phone screens will be stored in a locked drawer in a locked office and scanned into Box.

6.2 Data: Copies of all assessments used in the protocol (including obsolete versions) will be included in the Regulatory Binder. For online assessments (e.g., the Posit Science Auditory Sweeps), directions to access the portal will be included. For measures sensitive to practice effects (e.g., HVLT, BVMT), we will use alternate forms. Practice effects between-groups are controlled for by the study design. A counterbalancing sheet has been established to ensure participants receive alternate versions of the forms in proper order.

For a complete Schedule of Events, please refer to Section 26.

Assessments that can be completed remotely have been indicated with an asterisk*.

Neurocognitive Assessments:

- MATRICS Consensus Cognitive Battery [MCCB, (59)]
    - Trail Making Test: Part A
    - Category Fluency (Animals Only)*
    - Brief Assessment of Cognition in Schizophrenia (BACS) Symbol Coding
    - Continuous Performance Test—Identical Pairs (CPT-IP)
    - Wechsler Memory Span (WMS) Spatial Span
    - UMD Letter-Number Span*
    - Hopkins Verbal Learning Test (HVLT) Learning Trials: Immediate and Delayed Recall*
    - Brief Visuospatial Memory Test (BVMT) Immediate and Delayed Recall
    - Neuropsychological Assessment Battery (NAB) Mazes
    - Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT)*
- Wechsler Test of Adult Reading (WTAR) (Baseline only)*
- Penn Emotion Recognition Test (61)*
- Penn Facial Recognition Test: Delayed Recall*
- Penn Prosody Identification [PROID, (62)]*
- Posit Science Auditory Sweeps Test*

Clinical and Functional Assessments

- Demographics*
- Substance Use Summary*
- Medical History review*

- Mini International Neuropsychiatric Interview (MINI) (Baseline only. Suicidality module not used to determine suicidality risk; C-SSRS will be used instead)*
- Structured Clinical Interview for DSM 5 (SCID) (Baseline only; only in cases where the MINI is not sufficient to deliver a clinical diagnosis)*
- Positive and Negative Syndrome Scale [PANSS, (63)]*
- The Quality of Life Scale—Abbreviated [QLS, (65)]*
- UCSD Performance Based Skills Assessment [UPSA-Brief, (49)]
- Social Functioning Scale [SFS, (66)]*
- Internalized Stigma of Mental Illness Self Report [ISMI, (67)]*
- Global Functioning Role and Social*
- Global Assessment of Functioning (GAF-M)*
- Clinical Assessment Interview for Negative Systems (CAINS) Self Report*
- Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) Scales*
- Temporal Experience of Pleasure Scale [TEPS, (71)]*
- Columbia Suicide Severity Rating Scale (C-SSRS)*
- Faux Pas*
- COVID19 Stress Screener*

Feasibility and Acceptability

- Post-Training Participant Survey (Post-Intervention only)*
- Participant Closeout Report (Post-Intervention only; only if the participant disengages from services and the study staff is unable to contact them to complete the post-training survey)*
- Post-Training Clinician Survey (Post-Intervention only)*
- Computer Utilization survey*

6.3 Release/Sharing:

Participants will be asked in their consent form whether they consent to the research team using their data for future research projects; this answer will be referenced before including the participant in other data sets.

BrainHQ assessment and training data will be collected and maintained by Posit Science to perform analyses and for the preparation of manuscripts, presentations, and other dissemination of results to the public. Additionally, Posit Science may use the data collected in this study for project development and quality assurance purposes. Posit Science may share the de-identified data sets with collaborators as they see fit. Please refer to Section 18.0 Confidentiality for information about the de-identification of study data.

Penn CNB assessment data will be collected and maintained by the University of Pennsylvania and may be used to perform analyses and to prepare manuscripts, presentations, and other dissemination of results to the public. Additionally, the University of Pennsylvania may use the data collected in this study for project development and quality assurance purposes. The University of Pennsylvania may share the data sets with collaborators as they see fit.

Assessment data may also be shared with other collaborators outside of the UMN, with the permission of the PI. If the collaborator is interested in using the BrainHQ data or Penn CNB data, permission from Posit Science or University of Pennsylvania must also be obtained. Outside collaborators will be required to enter into a Data Use Agreement with the PI, Posit Science, and the University of Pennsylvania, as applicable. Most likely a limited data set will be shared (e.g., date of collection will still be included), but the data set may be completely de-identified if required by the agreements. Data shared with any collaborator (UMN or outside) will never contain direct identifiers. Study staff will verify that the data set has no direct identifiers by having two staff members review the data set to ensure that all necessary information has been removed. The exact methods of access and the data shared will be detailed in the data use agreements. These records will be maintained for a minimum of two years after the expiration of the agreement.

De-identified study data will be shared with our collaborators at University of California San Francisco. Study staff will upload data to a shared database in UCSF's REDCap server. This data will not contain participant identifiers, but will contain appointment dates. Staff at UCSF may use this data in analyses with the COTES study data (see study 1607S90201). If participants have authorized their data to be used in future studies, the UCSF team may also use this data for additional analyses.

Video/audio data will only be shared with outside collaborators if the participant has authorized for their recordings to be used for other research projects. Collaborators will need to have the permission of the investigators and an appropriate data use agreement in place to ensure the protection of participant identities. Appropriate restrictions for use of the data will be included in the terms of the data use agreement. As much as possible, collaborators will only be given Viewer access to the files and will not be able to download the video/audio file to an external device. Study staff will regularly check who has permissions to view the video/audio files and will remove access for any individuals who no longer need to view the files.

Some participants may authorize that the study team can use their video or audio recordings in scholarly presentations or publications In these instances, the study team will attempt to limit the ability to identify the participant while still providing

meaningful data to the intended viewers. Examples of methods used may include blurring the participant's face or using only the audio for video clips.

Additionally, study participants may authorize that their audio or video files can be used for training research staff in the future. In this case, trainee staff can view their clinical assessments to learn how to conduct interviews and to compare assessment scores against the original assessor.

Some assessment measures are used in other studies in the Department of Psychiatry (e.g., the MINI 7). In order to reduce the time and effort involved in repeating these measures, participants will have the option to allow the study team to share the information from these measures and computerized tests with other study teams. If they agree, staff will ask if they are participating in any other research studies in the Department of Psychiatry. Staff will reach out to that study team to see if they could share study information. Similarly, if the participant joins another study after enrolling in this one, the study team could share information from the same study activities with that study team. If the participant is also enrolled in the COPRR study, data may be shared with this database and with other research teams through this platform. This option to share data will be included in the optional elements of the consent form.

7.0 Sharing of Results with Participants

7.1 Information regarding individual research results will not be shared with study participants. Participants will be informed that if they are interested, they can see the results of this research study and other studies conducted by Dr. Vinogradov on her study website and on clinicaltrials.gov.

8.0 Study Duration

8.1 Participants will be in the active intervention phase for 6-12 weeks. Overall study participation will last approximately 10-12 months. We anticipate requiring three years to enroll all study participants and a total of four years to complete all study procedures. Data analysis will take an additional one to two years.

9.0 Study Population

9.1 Inclusion Criteria:

- Clinical diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder, major depressive disorder with psychotic features, bipolar disorder with psychotic features, psychosis disorder not otherwise specified, or unspecified schizophrenia spectrum disorder, and started receiving treatment services at a First Episode Psychosis Program using the NAVIGATE model within the last two years

- Good general physical health
- Aged between 16 and 35 years (inclusive)
- Fluent in spoken and written English
- No neurological disorder (diagnosis of Autism Spectrum Disorder is allowed)
- Achieved clinical stability, defined as outpatient status for at least one month prior to study participation and on clinically stable doses of psychiatric medications for at least one month prior to baseline assessments; participants may enroll in the study and complete the screening visit before having clinically stabilized medication regimen. The PI may review changes to the participant's medication regimen and allow the participant to proceed to baseline assessments, if the changes are deemed to be minimal
- Women who are pregnant or breastfeeding may participate in this study.
- The PI may make a determination to enroll participants from a program that employs a similar treatment model but is not considered a First Episode Psychosis Program (such as an early mood disorders program) on a case by case basis, if the clinic uses the NAVIGATE model and the participant meets all other eligibility criteria

9.2 Exclusion Criteria:

- Unable to provide informed consent
- Participated in significant cognitive training programs within the last three years
- Clinically significant substance abuse that is impeding the participant's ability to participate fully during recruitment, assessment, or training (is unable to remain sober for assessments and training).
- Prescribed >0.5mg daily benztropine (Congentin), >25mg daily diphenhydramine, or high doses of clozapine (>500 mg po qd) or olanzapine (to be determined on a case by case basis).
- Risk of suicidal behavior, as indicated by the C-SSRS or clinician judgment. Risk of suicidal behavior is defined as:
    - Active suicidal ideation at screening or baseline, or
    - Previous intent to act on suicidal ideation with a specific plan, preparatory acts, or an actual suicide attempt within the last 3 months

9.3 Screening: Participants will be referred from the First Episode Program at the University of Minnesota Physicians Psychiatry Outpatient Clinic or Mental Health Neuromodulation Clinic, Hennepin County Medical Center, NorthPoint Health and Wellness Center, or other clinics following the NAVIGATE model, per PI review and approval. Upon first contact, study staff will review the phone screen and ask

questions to determine potential eligibility. Diagnoses and suicidal risk will be determined during intake assessments. Participants who did not initially qualify for the study due to medication changes, hospitalization, or risk of suicidal behavior may be put on hold after intake procedures are completed.

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 22.5 for the procedures to determine capacity to consent.

10.3 Additional Safeguards: Some of the participants in this study will be patients of the Principal Investigator, Sophia Vinogradov, or Co-Investigators on the study. Other participants may have this study introduced to them by their clinical care team inside of the First Episode Programs/NAVIGATE teams at the recruiting sites. To mitigate the possibility of coercion upon their patients, clinical staff will not be involved in the recruitment process. Potential participants from the UMP Outpatient Psychiatry Clinic and Mental Health Neuromodulation Clinics interested in research opportunities will be introduced to a member of the study team or the Department of Psychiatry Research Recruitment and Outreach Specialist. These staff will provide a general introduction to the study and recruitment materials; research staff may also complete the screening questionnaire and set up a consent appointment.

Minors who are asked to participate in this trial may only proceed with study procedures with the consent of a parent or legal guardian. Please refer to section 21.2 for Consent/Assent procedures. This is a minimal risk study and children do not face greater risk by participating than adults.

11.0 Number of Participants

11.1 Number of Participants to be Consented: We will recruit 235 participants (for a targeted 150 completers).

12.0 Recruitment Methods

12.1 Recruitment Process: Study staff will post flyers, brochures, and contact cards at recruiting locations to advertise the study and connect with treatment providers to educate them about the study.

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.

Outpatients seen at the UMP Psychiatry Clinic or Mental Health Neuromodulation Clinic and research participants in the Department of Psychiatry Ambulatory

Research Center are asked to complete a Consent to Contact for Research form to indicate if they are interested in being contacted for future research opportunities. These individuals will be added to a recruitment registry managed by the Department of Psychiatry. This registry will contain their name, contact information, and basic demographic information such as age and diagnosis. Study staff will request the contact information for those who have signed the consent form and meet basic inclusion criteria for the study.

Additionally, the Psychiatry Department has a Research Recruitment and Outreach Specialist who is available to UMP clinic staff as a neutral party to 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, and ask patients to sign a Consent to Contact for Research form.

Clinicians who see patients with psychotic illnesses within recruiting clinic locations may discuss this study with their clients to see if they are interested in participating. If the provider is an investigator on the study, they will not describe the study in detail, but will make an introduction to a member of the study team to provide information about the study. Clinic staff may facilitate the signing of the Consent to Contact for Research form, provide recruitment materials, and arrange communication with the study team. Clinic staff may ask their patients if it is okay to send their patient's contact information to the study team; if the patient agrees, the clinician can send the study team messages through EPIC or via encrypted emails in order to facilitate communication.

Study staff will also regularly attend UMP Strength program and UMP NAVIGATE clinic meetings to discuss current participants' clinical status, and they may use this time to ask providers if they have any patients who they think may be eligible and interested in participating in the study; if a participant is enrolled from another UMP NAVIGATE clinic, staff may attend those clinic huddles as well. To facilitate this discussion, study staff may use EPIC to check the provider's schedule to see if they have a visit with a patient that has not been contacted by the study team (or indicated that they are not interested in research). They will not be able to see any other details about the patient, such as date of birth, contact information, diagnoses, medications, etc. Study staff may send secure messages to providers in EPIC to ask if their scheduled patient may be eligible/interested in the

study. Clinicians may contact the study team during/after an appointment to ask them to meet with their patient to discuss research opportunities. In these cases, a member of the team will meet with the patient and escort them to a private room in the ARC or the St. Louis Park clinic to discuss the study, conduct a phone screen, and set up consent visits for eligible/interested individuals.

Study staff will also establish ways to regularly connect with providers at HCMC and NorthPoint to facilitate the recruitment of patients to this study. Study staff are not able to attend clinic huddles, but they will regularly reach out to clinic staff via phone or email to see if there are any new potential participants and to ask if they need additional recruitment materials. Staff may travel to the site upon request from the clinic team to speak with clinicians and/or potential participants who are interested in learning more about the research.

COVID19 Procedures
Recruitment will continue for this protocol during COVID19 social distancing procedures. Study staff may continue to follow the procedures outlined above, but they will not attend in-person visits with clinic staff or meet potential participants face-to-face. Instead, they will communicate through email, phone call, EPIC and Zoom as applicable to facilitate recruitment.

During this time, it is anticipated that enrollment will slow down. In order to keep potential participants interested in the research, study staff may keep them engaged by regular communications (no more than once per week). Study staff may reach out to interested individuals by phone, email, or mail, based on participant preference. Potential participants may also receive a "University of Minnesota Citizen Scientist" hat or post-cards. These items will not replace financial payment.

12.2 Source of Participants: The First Episode NAVIGATE Programs at the UMP Psychiatry Outpatient Clinic, UMP Mental Health Neuromodulation Clinic, HCMC, NorthPoint Health and Wellness Center, and other clinics following the NAVIGATE model, per PI review and approval

12.3 Identification of Potential Participants:

Participants may be identified to participate in research in several methods:

- Participants may self-identify by using posted recruitment materials from UMP clinic lobbies, websites (listed below), or from community events
- Clinicians in the NAVIGATE programs at HCMC, Northpoint, UMP Psychiatry Outpatient Clinic, UMP Mental Health Neuromodulation clinic, or other clinics following the NAVIGATE model (per PI review and approval) may refer their patients to the study team

- Participants may be recruited from the Department of Psychiatry Recruitment Registry, based on their basic demographic information included within the registry
- COPRR Database
- Participants may be referred to the study team by the Department of Psychiatry Research Recruitment and Outreach Specialist
- Study staff may view clinic schedules to see the names of patients that clinic providers will be seeing, in order to communicate with the clinician during clinic meetings or through secure messages in EPIC, to ask if the provider believes the patient would be eligible for the study, and to remind them to ask their patient if they are interested in the program. Study staff will not view information beyond the patient's name and time of appointment for recruitment purposes

12.4 Recruitment Materials:

- Flyers
- Brochure
- Contact cards
- A "University of Minnesota Citizen Scientist" hat
- Postcards signed by staff members
- Phone Screen
- Website postings
    - Clinicaltrials.gov
    - https://vinogradovlab.umn.edu/
    - Psychiatry.umn.edu/research
    - Study Finder
- Psychiatry Clinic TV

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 appointments and when they achieve computer training milestones. 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. The schedule for payment is detailed in the sections below. 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.

Compensation for Assessments:

- $80 for completing baseline assessments
  - $15 for completing the Consent and diagnostic interview
  - $35 for completing the Clinical and Computerized Measures Interview
  - $30 for completing the Neurocognitive Assessment
- $70 for completing post-intervention assessment + $50 bonus = $120
  - $35 for completing the Clinical and Computerized Measures Interview
  - $35 for completing the Neurocognitive Assessment
- $70 for completing 6 month follow-up assessments + $50 bonus = $120
  - $35 for completing the Clinical and Computerized Measures Interview
  - $35 for completing the Neurocognitive Assessment
- Total compensation earned for completing the study assessments: $320

Compensation for Computer Training

- Participants who have been randomized to either the TCT or GCE arm will receive $25 for every five hours of cognitive training they complete. If the participant completes all 5 suggested hours for all 6 weeks of the treatment phase (30 hours total), they can earn up to $150. Payment will be made whenever the 5 hour training milestone has been achieved. Participants randomized to the computerized training arms can earn up to $470 total.

Reimbursement for parking:

- Participants may be reimbursed for parking expenses for visits at the Riverside campus. Participants will be asked to keep copies of their receipts from parking and provide them to study staff so that they can have the amounts loaded onto their ClinCard. If participants lose their receipts, study staff will work with them to find a solution, but they may not be able to be reimbursed for their parking.

Participants may request to receive their payments in installments rather than as a “lump sum” after both assessment appointments are complete. Participants who do not complete all of the study activities for an appointment will be given prorated compensation for the portions that they did complete.

If a participant is asked to repeat any assessments (e.g., data was lost due to a technical difficulty), the participant will be eligible to receive compensation for the assessment a second time. Study staff will calculate the appropriate compensation based on the amount of time that the participant spent repeating appointments.

If a participant is asked to wait for a significant time during a scheduled appointment slot and study activities do not occur, the PI may determine to provide compensation for the participant's time spent waiting. For example, if a participant waits for an appointment to begin but technical difficulties prevent the procedures from being completed and the participant is sent home, the PI may provide the participant with compensation, including reimbursement for parking. Reimbursement will be provided at a rate of $15/hour, rounded up in 15 minute increments.

If a participant agrees to share information between study teams, their compensation will not be impacted.

Due to the social distancing procedures implemented during the COVID-19 outbreak, some participants will not be able to complete the full assessment battery during their appointment windows as some activities can only be completed in person. These participants will still be offered full compensation for completing the visit, including bonuses. If they are invited to complete the in-person assessments when social distancing procedures are lifted, they will be offered compensation at the same prorated amount used for repeated assessments.

13.0 Withdrawal of Participants

13.1 Withdrawal Circumstances: Participants will only be disqualified for this trial if there is a question of the continued safety of their participation or if they are unable to adhere to study rules. Should participants have adverse events, their continued participation will be reviewed on a case-by-case basis by the investigators and the PI will determine whether they should be withdrawn from the study.

Additionally, if the FEP participants show a worsening of clinical status, particularly if it affects their capacity to provide continuing consent, their clinical status will be revisited and their eligibility to participate determined. Participants who show a diminished capacity to consent will be placed on temporary hold (30 days); if they are not recovered at the end of this 30 days, the PI may make a case-by-case determination to continue the participant's hold period or to withdraw them for the study. The participant will also be placed on a 30 day hold following hospitalization for psychiatric reasons. As fluctuating symptoms are a known risk of psychosis, participants who are hospitalized for psychiatric reasons will not constitute a promptly-reportable event to the IRB.

If a participant reaches the age of majority during their participation in the trial and is unable to display capacity to consent upon assessment, they may be withdrawn from the trial.

In cases where participants were loaned iPads and the iPads are lost or broken due to neglect or misuse, the study team may determine that they cannot be loaned another iPad and will withdraw them from the intervention phase of the study.

If we find a participant is legally committed to treatment during their time in the study, we will continue the study as normal, as long as the PI, the participant and their clinician believe it is in their best interest. When a member of the study team learns that a participant was placed under legal commitment, they will reach out to the participant's provider to gather additional information on the participant's clinical status and learn from the provider whether they believe the participant can continue with research activities. This information will be relayed to the PI, who will determine whether the participant may resume study activities (following re-assessment with the UBACC), if they should be placed on a temporary hold until symptoms improve, or if they should be withdrawn from the study. This decision will be documented in the participant's study file.

13.2 Withdrawal Procedures: In the case where a participant is withdrawn from the study for misuse of the study iPad, they will be asked to provide post-training and 6 month follow up data. If a participant voluntarily withdraws from the training, they may also be asked to provide post-training and 6 month follow up data, if they are willing. For participants who are withdrawn from the study due to worsening clinical status or adverse events, the investigators will determine on a case-by-case basis if the participant will be asked to provide any further data when they have reached clinical stability. In cases where the participant's capacity to consent is diminished or if they are not safe to participate, they will not be asked to provide follow up data.

Any data that had been collected prior to a participant's termination or withdrawal will be kept and used in the data analysis.

14.0 Risks to Participants

14.1 Foreseeable Risks:

- 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 1-4 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. Refreshments may be offered during longer appointment sessions.

- Risks of Computerized Training: Participants may become frustrated or fatigued when participating in their computerized training program. To mitigate these risks, we remind participants that they should only complete 60 minutes of training per day, 5 days a week to prevent them from feeling overburdened. Additionally, they may take breaks in their training sessions if they need to. The programs are self-adaptive to adjust difficulty level to approximately 80% success rates for individuals, which should help prevent feelings of frustration during the training programs.
- Randomization Risks: Since participants are randomly assigned to their intervention arm, they may receive an intervention that is less effective or has more side effects than the other study interventions, or other available treatments. There is also the chance that they will not receive any cognitive training at all during their participation in this study. However, the risks of randomization are not greater than minimal risk.
- Confidentiality Risks: Participation in research will involve a loss of privacy due to the nat data collected during training sessions. However, records will be handled as confidentially as possible. Please refer to sections 6.0 Data Banking, 16.0 Data Management, and 17.0 Confidentiality for further information about how PHI is handled in this study.
- Risks of Email communication: Participants will be able to opt in to communicating with study staff via 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 a 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.

Participants do not have to opt in to email communication in this study. However, they must agree to email communication to complete remote study activities. . If they change their mind about communicating via email, they can notify staff at any time about their communication preferences.

- 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 do not have to opt in to 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.

  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.

15.0 Incomplete Disclosure or Deception

15.1 Incomplete Disclosure or Deception: N/A

16.0 Potential Benefits to Participants

16.1 Potential Benefits: There are no direct benefits to individual participants for taking part in this research. Subjects who participate in the study may derive benefit from the detailed assessments of clinical and cognitive status and from participation in either of the experimental interventions. If the experimental condition proves to be beneficial to psychosis participants as a group, then this will be extremely helpful in the design of future remediation programs for patients. This study is not a substitute for treatment or therapy and participants will continue to see their doctors as normal.

17.0 Data Management

17.1 Data Analysis Plan:

To test Hypotheses 1, 2, and 4, we will use Repeated-Measures Analysis of Variance (ANOVA). The measures at baseline, post-training and follow-up (i.e., Time) will be entered as the repeated within-subjects factor, and intervention group (TCT, GCE, TAU) will be entered as the between-subjects factor. To control for Type-I error rates, group differences will be tested using composite general cognition, verbal learning/memory, and social cognition scores rather than individual measures. For Hypothesis 3, change scores will be computed for the composite scores by computing the difference between follow-up and baseline. Pearson correlations will then test associations between composite index change scores. Because of potential non-independence between estimated correlation correlated measures (68). In addition to examining pairwise difference between correlation measures, we will evaluate homogeneity across measures, also using bootstrap methods. To test Hypothesis 5, Chi-Square Test will be used to test the percent of subject who complete >20 or <30 hours of training. Hypothesis 6 will be tested with Independent Samples T-test. We will conduct both a per protocol analysis on participants who complete a minimum of 20 hours of training, and an intent-to –treat analysis on all randomized participants.

Prior to formal statistical testing, the assumptions of normality and variance homogeneity will be assessed for all variables. Where significant departures occur, appropriate transformations will be applied. Such departures have generally been absent or minimal in our previous studies, and will be corrected by simple arithmetic functions, if required. Through randomization, we anticipate that the participant groups will be comparable in terms of age, education, medication status (CPZ equivalents), and symptom severity. If significant differences exist, we will statistically adjust for these effects via inclusion as covariates in the

Repeated Measures ANOVA analyses. Models will appropriately account for factors that vary with time on study (e.g. medication status), and will account for possible nonlinearities in responses as well as potential interactions with other factors. Prior studies neither support nor negate significant differences in intervention effect between males and females, or between different ethnic subgroups. Thus, after testing our hypotheses as stated above, we will carry out additional analyses on the effects of the treatment intervention by sex and ethnic group.

17.2 Power Analysis:

The power analysis described below is based on the following measure of effect size from our study of TCT in recent-onset schizophrenia vs. a computer games control condition: After 40 hours of TCT training, the Global Cognition d = 0.66. As a comparison, the mean effect size for Global Cognition from a recently reported meta-analysis of 40 studies of cognitive training in schizophrenia is 0.45 (8). These considerations lead to sample size estimates of 50 TCT and 50 GCE participants who complete training and 6 month follow-up with an estimated power of 95% to detect the effect of TCT at post intervention at alpha level = 0.05, and power of 90% to detect the effect at 6 month follow-up at alpha level = 0.05.

The power analysis for social cognition training is based on a recent meta-analysis of computerized cognitive training in schizophrenia which found a significant effect size of d = 0.64 (51). These considerations lead to sample size estimates of 50 TCT and 50 GCE participants who complete training and 6 month follow-up with an estimated power of 94% to detect the effect of TCT at post intervention at alpha level = 0.05, and power of 89% to detect the effect at 6 month follow-up at alpha level = 0.05. These estimates account for attrition.

17.3 Data Integrity:

Missing data will be handled in two ways. First, any participant who discontinues the study prior to completion will be replaced by the next eligible participant. The number of participants dropping from each intervention 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 participants 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.

We will ensure the accuracy of all data in this study by using a vigorous dual entry system. All scores will be verified by two separate graders on the physical summary score sheet kept in the participant binder. If there are discrepancies between scores, a third party grader will come in and verify which score is correct. If there continues to be a discrepancy, the three graders will meet and discuss the variation in their scores until they can come to a consensus. When the scores are agreed upon, the data will be entered into REDCap by two separate individuals. Those involved in the data entry process will be assigned to one of two REDCap data entry accounts. Once each account has entered the data, a third person will compare the entries and resolve any discrepancies between the two.

Additionally, video/audio footage of assessment appointments will be reviewed by study staff to confirm ratings and ensure inter-rater reliability for assessments of symptoms and behavior. This will ensure that our data is accurate and consistent across the group.

18.0 Confidentiality

18.1 Data Security:

University of Minnesota study staff will complete HIPAA training, Data Security training,, and the CTSI Research Foundation Training, as applicable to their role, prior to interacting with study data. Documentation of this training will be included in staff personnel records.

All digital records maintained on Posit Science, University of Pennsylvania, UCSF, and UMN servers will require a username and password to access study information. These servers are secure and will require permissions from the study team to access.

All physical records will be maintained in locked cabinets in locked offices, until the appropriate time at which documents may be shredded. Access to these cabinets will be limited to the study team. All physical consent documents will be stored in a separate binder to remove PHI from the participant's assessment data. Some PHI is collected during appointments, such as the demographics form. When data entry for the visit is complete, study staff will remove the sheets containing PHI and place them in the same binder as the consent forms.

Consent documents may also be collected digitally using the UMN REDCap servers. Paper consent forms will also be maintained digitally by scanning the documents

into Box. Consent documents will remain on these servers for a minimum of 6 years after the completion of the study.

REDCap will contain all outcome data from clinical and neurocognitive assessments, including the CPT-IP. No participant identifiers are uploaded into the database, but appointment dates are recorded.

BrainHQ training and assessment data collected by Posit Science will not contain direct identifiers, as members of the study team will create log ins for participants. The web browser and iOS applications used in the study will not store any data locally on participant or lab devices, but will immediately transfer to Posit Science servers. Geolocation/geographic information will not be stored. IP address data is stored only in memory and in request logs, and is used for technical support and troubleshooting, but not persisted with the participant's data. Data are uploaded using SSL over encrypted channels to secure servers every 30 seconds. Therefore, security of electronic data is ensured at the level of the server, the user, and the database. When the study team requests or extracts data from Posit Science, they will create a limited data set; the location data will be removed, but the date of data collection will remain. Posit Science will maintain all data collected during the study indefinitely within their servers, but identifying information will not be shared with outside collaborators or in publications. The University of Minnesota and Posit Science have a Business Associates Agreement in place to allow for the sharing of PHI between institutions.

The Penn CNB will not collect direct identifiers; however, the participant’s date of birth will be entered into the web portal to determine age at time of assessment. Date of data collection is also stored. The Penn CNB runs on a Macintosh OS X operating system which is updated on a regular basis for security vulnerabilities. A firewall runs on the server which only allows web traffic which has been encrypted by the TLS 1.0 standard using 128 bit encryption keys to pass to and from the server. All data collected by the server is stored in a MySQL database which is behind the same firewall. Passwords of administrators are encrypted using the md5 algorithm inside of the MySQL database. All data collected is backed up on-site to an encrypted external hard drive and remotely over an SSL encrypted channel for disaster recovery purposes. The system is built with stringent safeguards in place so that Principal Investigators and their designated researchers are only able to view data collected on their own research participants. Study staff will extract the data from the Penn CNB servers to UMN Box at interim and final analyses. The participants’ date of birth will be removed from the dataset at this time. The data will remain on UMN Box indefinitely.

Many participants will communicate with the study staff via email. These emails will be maintained on a dedicated departmental email account until identifying information is deleted from study records. In some cases, communication with participants may contain significant information that will be saved as part of the

individual's study record. In these cases, the emails will be saved to a dedicated folder within Box specific to that participant.

Some participants may choose to text the study team. These text messages will be regularly deleted from the University cell phone. Participant names will not be saved in the contact log, but the participant's ID number will be associated with their phone number to allow staff to identify the person that is to be communicated with. Similar to emails, texts that provide significant information will be saved as part of the individual's study record by saving screenshots of the conversation and sending them to the study email account.

Participants will be registered within the ClinCard Greenphire system to receive their study compensation. To register the participants, study staff will enter the participant's full name and mailing address. Participants will be notified in their consent form that ClinCard will have access to this information. ClinCard is a HIPAA compliant server and the UMN has a BAA to allow sharing of PHI with this institution.

Participants will be registered in OnCore. If a participant is a patient in the Fairview Health system, their MRN may be associated with their study record. In these cases, their medical records will indicate that they were enrolled in this study. The clinical care staff who view their medical record will not be able to see any consent forms or study data within the patient's electronic medical record, but they will be able to see the name of the study and the contact information for the research staff. A copy of this consent form will not be included in their educational or employment records.

Video and audio data will be stored on UMN Box servers for future analyses and staff training. Study staff may provide access to these files to collaborators; data use agreements may be required prior to providing access. Study staff will manage access regularly by reviewing the collaborators and their permissions levels, and making changes as appropriate. Collaborators will preferentially be given viewer-only access to prevent downloading files from Box onto external devices. However, different terms may be established within a data use agreement, if needed.

All computerized assessments will be conducted on computers managed by AHC-IS; some paper forms will be scored on these computers also. Study data will regularly be deleted from the computer hard drives.

Most participants will complete remote training using UMN iPads under AHC-IS management. All loaned iPads will have GPS tracking enabled via "Find my iPad." If a device is lost or stolen, the study team will use this service to remotely wipe and lock the iPad. Location data will not be used to track down or locate the iPad, nor will it be delivered to any outside parties. Once the iPad is returned, study staff will erase the memory to clear any data that was generated and stored by the

participant. Some participants may have their own iPad and they may choose to use it instead of loaning a lab-owned iPad if they prefer.

Identifying information will be maintained in the participant consent forms, the REDCap demographics form, Box, and OnCore for a minimum of 6 years after the study completion, as required by HIPAA regulations. When study staff are ready to permanently delete identifying information, they will work with officials in UMN OIT, REDCap, and OnCore to ensure that the data are permanently deleted.

When data will be de-identified or redacted, study staff will ensure that all PHI is removed from the file in question before permanent storage. The redaction will be verified by a secondary staff member.

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

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

19.1 Data Integrity Monitoring

The PI will be responsible for all project operations and for ensuring the integrity of the research procedures and data collected. Investigators and/or data managers will monitor the data collected and conduct data integrity checks. Data in REDCap 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 capacity to restore to the original entry if necessary. Additionally, when the full data set (REDCap, Posit Science, Penn CNB data) is migrated to Box for permanent storage, a master data set that has had identifiers removed will be locked. If there are any questions about data points, the investigators and/or data manager will contact study staff to resolve any queries.

All regulatory and participant research files will undergo monitoring by University of Minnesota Clinical Translational Science Institute (CTSI). Monitors will also ensure that the study is conducted in accordance with the protocol and inclusion/exclusion criteria as approved by the IRB. Monitors review study materials (documents, records, drug/device accountability, Case Report Forms, etc.) to assure that the study is conducted, recorded, and reported in compliance with FDA Good Clinical Practice. Their goal is to partner with investigators to promote and facilitate compliance with Good Clinical Practice through: regular monitoring visits; quality assurance; data query resolution; review of study regulatory files; adverse Event/Serious Adverse Event (AE/SAE) reviews; compliance consultation services; signed informed consent/HIPAA documents; Case Report Forms (CRFs); Medical records (for AE/SAE); regulatory binders; communications with FDA/IRB; and Investigational Product (IP) distribution logs.

19.2 Data Safety Monitoring

This is a minimal risk trial and we do not anticipate any adverse events from participation in the study. Nonetheless, to follow best practices for clinical research, we will follow the Participant Safety Monitoring Plan outlined below to review Unanticipated Problems and Adverse Events.

Vinogradov Lab Participant Safety Monitoring Plan

Participants will be screened for eligibility according to the procedures described in Section 8.3 Screening to avoid unnecessary exposure to risk.

Study Coordinators and Clinical Assessors will have regular contact with research participants described in Section 5.2 Study Procedures. Participant safety will be monitored using assessments defined in Sections 5.2 Study Procedures and 6.2 Data. Study Coordinators and Clinical Assessors will be trained by Vinogradov Lab Management to recognize symptoms that indicate worsening clinical status, suicidal and homicidal ideation, self-harm, and abuse or neglect.

Study Coordinators will deliver regular participant updates to the PI and Co-Is at the weekly Vinogradov Lab Meeting and other team meetings. In the case where a Study Coordinator misses a team meeting, they will coordinate with their supervisor or an Investigator to deliver participant updates.

If a Study Coordinator or a Clinical Assessor becomes aware of a significant change in functioning or behavior, or if they are concerned for the welfare of the participant or others, they will report their findings to an Investigator as soon as possible. If there is an immediate safety concern, the Investigator will initiate the Crisis Protocol. If there is no immediate concern, the case will be discussed with the PI at the next meeting. The Investigators will follow the procedures outlined in Section 12.0 Withdrawal of Participants and Section 21.6 Cognitively Impaired Adults, as applicable.

If the Study Coordinators or Clinical Assessors learn of potential or confirmed abuse or neglect of a child or a vulnerable adult, the Investigators will consult with the University of Minnesota Office of General Counsel to determine whether they need to follow Mandated Reporting procedures.

Unanticipated Problems, Adverse Events, and follow up will be documented via Notes to File signed by the PI and stored in the participant's record in Box. The PI will determine whether the event needs to be reported to the IRB, per the HRP-103 Investigator Manual.

20.0 Provisions to Protect the Privacy Interests of Participants

20.1 Protecting Privacy:

During the consent discussion, participants will be notified that the study team may contact their provider under certain circumstances--determining eligibility, completing the Likert scale, mandated reporting instances, and when providing/receiving updates on health or study status.

Participants have the option to opt in to emails from study staff to set up appointments or to discuss their study participation. Similarly, participants may opt in to 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 in to 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.

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 1-4 week periods to avoid fatigue and stress.

When training new assessors, the trainee 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.

Participants will be asked if they agree to have their assessment appointments video or audio recorded for the following purposes: consensus of assessment ratings and supervision of assessment staff; training of new research staff in the conducting of assessments; answering other research questions after this project is complete. Participants can opt into any of these conditions. If they do not wish to give us permission to video or audio record their assessment appointments, it will not affect their participation within the study. Participants will have the right to stop recording at any time and will have the right to review the tapes made as part of the study to determine if they should be edited or erased in whole or in part.

The participant may choose to have a guest sitting in on their appointment with them, if they would like.

Participants will be asked if it is acceptable for study staff to discuss their study participation and health status with a member of their family or friend. If the person agrees, they will be asked to identify who the study staff may speak with.

If a participant is a minor, study staff will be authorized to discuss the logistics of study visits with the parent or legal guardian until the participant reaches the age of 18. Participants must give their permission to study staff to discuss details of study participation or their mental health with their parent or legal guardian. At this time, the participant will be able to indicate whether or not the details of study participation will continue to be shared with the parent or legal guardian. Parents/guardians will also be allowed to sit in on assessment appointments if the child agrees, but will be asked not to participate during cognitive assessments. They may help a child to provide historical information when completing assessments of functioning, behaviors, and symptoms. At the end of each appointment, particularly if sensitive questions about drug use, sexual activity, or self-harm were asked, the researcher may ask the guest to step out of the room so they can check if there was anything else that the participant left out due to the guest being present.

Participants will be notified in their consent forms that their data will be shared with Posit Science, the University of Pennsylvania, the University of California San Francisco, and ClinCard over the course of this study. They will be notified that identifying information is shared with these institutions and what agreements exist between UMN and these partners to protect their information.

20.2 Access to Participants: During the consent process, participants will provide consent for research staff to access their medical records for study purposes. We explain that we look only for the usage of specific medical services within the EPIC calendar and we access their diagnoses and medication lists. We will not read the notes or record personal details from the medical record in our charts. We ask for permission for wider access beyond this scope, but we explain that we will always

ask permission before going into a participant's medical records for other purposes than those previously described. Participants sign a consent form and a HIPAA Authorization to provide us permission for these tasks. In cases where there is a significant clinical event that may impact study performance or data integrity, the study team may reach out to the participant to ask their permission to view electronic medical records in EPIC.

21.0 Compensation for Research-Related Injury

21.1 Compensation for Research-Related Injury: If a participant is injured or made ill by study procedures, standard medical care will be made available to them. However, participants will be informed that any costs that are incurred will be billed to them or to their insurance and will not be covered by study funds.

22.0 Consent Process

22.1 Consent Process:

In-person consenting will take place in a private office at the University of Minnesota Department of Psychiatry, Ambulatory Research Center, in a private room in the Mental Health Neuromodulation Clinic in St. Louis Park. Remote consenting may occur via Zoom teleconferencing or telephone call. The participant may invite a friend or family member to the consent discussion if they wish. The research staff member will explain the study to the participants. After explaining the study, the participants will be allowed as much time as needed to review the HIPAA waiver and consent documents and ask questions before making the decision to participate. Participants can delay participation and return to sign the consent form at a later time. No participant will be under legal commitment at the time of their consent and surrogate consent will not be allowed. Consent will be captured in REDCap or on paper forms. Study staff will scan paper consent forms into Box, and the physical copy will be stored in the consent/PHI binder in a locked cabinet in a locked office.

For remote consent appointments, all consent forms will be included in a single REDcap database. Study staff will provide the participant with a link to the database via email prior to their appointment. If a participant currently enrolled in the study has not signed the Unsecure Email Authorization form, this link will be sent via ProofPoint. The REDCap consent form will contain periodic places for participants to place their initials to ensure that they are following along with the study team member as they review the document. At the end of the form, the participant will be able to sign the document using a mouse, trackpad, or tablet. As the study team member will not be able to co-sign the consent form, the participant will be asked to enter in the name of the person who

is leading the consent discussion. As a proxy signature, the study team member will provide the participant with a unique code; without this code, the REDCap survey will not save and the participant will not be able to complete the consent document. 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.

Participants may be asked to sign addendum consent forms if there have been changes to the study during their enrollment. Addendum consents will be captured at the participant's next study visit. If there have been multiple changes to the study during a participant's follow up period, they may be asked to sign multiple consent addendums. The study team may choose to have the participant complete a consent discussion with the full updated consent form instead, especially if there have been multiple updates to consent forms.

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

Participants who are patients at a non-UMP clinic will be asked to sign a Release of Information to allow study staff to speak with their clinical care provider to update them on their study status and to discuss their health status. Participants must give permission to staff to have contact with their clinician in order to be enrolled in the study. The ROI will be documented with the participant's other consent forms.

22.2 Waiver or Alteration of Consent Process:

Individuals who participate in the phone screen will be asked if study staff may keep their information to use for future research opportunities. They will inform individuals who fail the phone screen that this will involve storing their name, contact information, and the answers to the screening questions. These records will be maintained in paper format and digitally on Box. As most individuals completing the screen will be remote, we will only obtain verbal consent to store this document.

22.3 Participants Who Are Not Yet Adults (teenagers under 18 years of age):

Participants who are between the ages of 16 and 18 may participate in this trial with the permission of a parent or legal guardian. Participants will be asked to provide their birth date so that study staff can determine that they meet the age requirements for the study and if they will reach the age of majority while

participating in the study. Once participants reach the age of majority, they will be required to sign informed consent before continuing on with study procedures.

The consent discussion for minors will be similar to the discussion for adults described above. If the participant is a minor, they must have at least one parent or legal guardian present during the consent discussion. The minor will sign an assent form while the parent or legal guardian will sign a consent form. In cases where there have been changes to the protocol between visits, participants may be asked to sign addendum consent/assent forms, but study staff may also choose to complete a full consent discussion with an updated consent/assent form. Parents/guardians will sign the HIPAA Authorization for the child. Neither the parent/guardian nor the child will be required to complete a UBACC assessment.

Parents and adolescents may still consent and assent to the study remotely following the procedures described above. If the consent discussion occurs over phone rather than Zoom, the study staff will periodically check in with the parent and teen to ensure that both are still present for the whole conversation. The study team member will utilize two codes, one for the parent and one for the adolescent.

22.4 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 a modified version of the UCSD Brief Assessment of Capacity to Consent (UBACC) to adult participants. In our version of the UBACC, we did not include Question 10 as the risk of hospitalization due to research is unlikely, and there is no corresponding information in the consent document. If the participant scores less than a 14 on the UBACC, the study staff may offer one session of remedial education to cover the points that the participant missed. If the participant is unable to score a 14 or higher on the UBACC after this remedial education, the participant will not be offered participation in this study. Individuals who initially didn't pass the UBACC 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. 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 UBACC 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 again before continuing with study procedures.

The UBACC will be re-administered by the study staff if deemed appropriate. Examples of instances in which a UBACC may be re-administered include (but are

not limited to): participants are returning to the study after a 30 day hold after hospitalization; the study team learns that the participant has been legally committed after enrollment; the participant is exhibiting increased symptoms; and other instances in which the study team is concerned that the participant may not be able to consent to research procedures.

Participants will be asked to complete a modified UBACC for the addendum consent/assent. Participants will be required to score 75% or greater on consent addendums; the passing score required for each addendum UBACC will be indicated in the preamble of the assessment. The rules for re-administering the UBACC for insufficient scores are the same as for the primary UBACC.

23.0 Setting

23.1 Research Sites:

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

Recruitment will occur at the UMP Psychiatry Outpatient Clinic, UMP Mental Health Neuromodulation Clinic, HCMC NAVIGATE clinic, NorthPoint Health and Wellness Program, and other clinics following the NAVIGATE model (per PI review and approval). Additionally, potential participants may meet with study team members at recruitment events in the community.

24.0 Multi-Site Research

Sophia Vinogradov is the Co-PI of the sister study to this protocol. This study is listed with the IRB as “Community-Based Cognitive Training in Early Psychosis,” 1607S90201.

24.1 Study-Wide Number of Participants: 470

24.2 Study-Wide Recruitment Methods:

Recruitment and running of participants will take place at four Prevention and Recovery in Early Psychosis (PREP) clinic sites and two Bipolar Early Assessment and Management (BEAM) sites, run by Family Service agency of San Francisco (FSA). Al Gilbert is the CEO of FSA and the contact for the sites. PREP San Francisco County/BEAM SF is located at 6221 Geary Avenue, San Francisco, CA. PREP San Mateo County/BEAM SMC is located at 1108 South El Camino Real, San Mateo, CA. PREP Alameda County is located at 22971 Sutro St., Hayward, CA 949541. PREP Salinas/Monterey is located at 909A Blanco Circle Salinas, CA 93901. Nine to ten clinicians, administrative staff and research assistants work at each PREP/BEAM site. Each PREP/BEAM clinic has one conference room, four to six individual offices, one workstation and one group work space, with PCs, printers and office furniture to support clinical and administrative staff, as well as comfortable

waiting areas for clients. PCs at all PREP/BEAM sites are networked for clinical data entry into a shared database.

Study RA's will attend weekly team meetings at the PREP/BEAM clinics that discuss all clinic clients in order to identify potential participants eligible for recruitment and to exchange information with clinicians regarding clinical status of active participants as relevant to study participation or team treatment planning (e.g., recent hospitalizations, relapses, incarcerations). RAs will not record any information on clinic clients who have declined study participation. All information is considered confidential and will not be shared outside the team.

Eligible participants who have enrolled in the PREP/BEAM Programs in San Francisco, San Mateo, Salinas/Monterey or Alameda will be recruited. Case managers/therapists at PREP/BEAM will inform their clients about the existence of the study. If the client expresses interest in participation, they will be referred to the staff member coordinating recruitment.

The COTES Tear-Away Poster (in Other Study Documents) will be posted at each of the four PREP sites from which we are recruiting participants, in an area visible to PREP/BEAM clients.

With their permission, research staff will communicate with enrolled research participants via text messaging using Google Voice. Research staff will use text messaging to facilitate scheduling appointments. To ensure that there is no loss of privacy or confidentiality, research participants will be informed that these methods of communication are not secure and that we will not be communicating any other information by these means. Google has received security certifications such as ISO 27001 certification and SOC 2 and SOC 3 Type II audits to demonstrate compliance with security standards. Research staff will refrain from stating any identifying information.

All participants who self-refer, are referred to or recruited by the co-P.I.s or their team will be assessed via brief interview to determine basic eligibility. Once determined to meet basic eligibility, potential research volunteers will then be asked to come in for an intake appointment to learn more about the study where they will have the study fully explained to them, give written informed consent, and (if they have agreed and given informed consent) receive the first part of their baseline assessments.

24.3 Study-Wide Recruitment Materials: N/A

24.4 Communication Among Sites:

The investigators of these studies participate in biweekly phone calls to check in on study progress. They discuss recruitment goals and progress reports. Additionally, they discuss any changes to the study procedures, study staff, or anything else that

would impact the collection of study data, and ensure that all study procedures are being followed. If interim analyses are conducted, they will be discussed during these meetings.

The assessors participate in a biweekly supervision meeting where they discuss any issues or questions that came up during participant interviews and how to interpret and rate behaviors.

Additionally, study coordinators participate in weekly meetings to discuss recruitment, participant engagement and retention, assessment administration, and other issues or problems that arise during the study.

Issues of non-compliance, reportable incidents, and adherence to federal regulations will be discussed at all of the calls above. Each site is responsible for reporting to its own IRB. Incidents requiring reporting at the UCSF site will not be reported to the UMN IRB outside of continuing review, as the UCSF is the IRB of record. No participants from UCSF are followed or identified at the UMN location.

Additionally, investigators and study staff are in direct contact via email consistently and quickly communicate any issues that need immediate attention.

25.0 Resources Available

25.1 Resources Available:

- Recruitment: As we will be recruiting participants from several NAVIGATE clinic sites for a period of three years, it is feasible for us to reach our recruitment goal of 150 participants with complete data by the end of this study. Each recruitment site sees between 20-100 patients per year that would potentially qualify for this study.
- Facilities: We have two 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.

  We have 6 iPads which can be loaned out to research participants to complete their cognitive training. We expect that approximately 30% of participants will have their own device and will not need to borrow an iPad from the lab. We may acquire additional iPads for a total of 15 if the rate of recruitment requires more devices to be loaned out to participants.

  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 one laptop for study assessment administration which will also be connected to the UMN secure networks via Ethernet. We have the necessary facilities to print participant binders and the required supplies to administer rating scales such as the UPSA and MCCB.

- 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.

26.0 Schedule of Events

Study Task	Screening/Baseline[1]			Intervention Phase (6-12 weeks)[2]	Post-Training Assessments[1]		6 Month Follow Up[1]	
	Screening	V1	V2		V3	V4	V5	V6
Phone Screen	X							
Consent	X							
UBACC	X							
HIPAA	X							
Demographics	X							
Substance Use Summary	X				X		X	
Mini International Neuropsychiatric Interview (MINI)	X							
Structured Clinical Interview for DSM 5 (SCID)[3]	X							
Computer Utilization Survey	X							
Wechsler Test of Adult Reading (WTAR)	X							
Review of Medical History and Medication List[4]	X				X		X	
Resource Utilization Survey[5]	X				X		X	
Columbia Suicide Severity Rating Scale (C-SSRS)	X				X		X	
Positive and Negative Syndrome Scale (PANSS)		X			X		X	
The Quality of Life Scale—Abbreviated (QLS)		X			X		X	
Social Functioning Scale (SFS)		X			X		X	
Global Functioning Role and Social		X			X		X	
Global Assessment of Functioning (GAF-M)		X			X		X	
COVID19 Stress Screener		X	X[9]		X	X[9]	X	X[9]
Penn Facial Memory Test (Immediate and Delayed Recall)		X			X		X	
CAINS (Motivation and Pleasure Scale: MAPS) Self-Report		X			X		X	
CPT-IP		X			X		X	
Prosody Identification (PROID)		X			X		X	
Penn Emotion Recognition Test		X			X		X	
Internalized Stigma of Mental Illness		X			X		X	
Posit Science Audio Sweeps		X			X		X	
HVLT Learning Trials (Immediate and Delayed Recall)			X			X		X
NAB Mazes			X			X		X
Study Task	Screening/Baseline[1]			Intervention Phase (6-12 weeks)[2]	Post-Training Assessments[1]		6 Month Follow Up[1]	
	Screening	V1	V2		V3	V4	V5	V6
WMS Spatial Span			X			X		X
BACS Symbol Coding			X			X		X
MSCEIT—paper and pencil version			X			X		X
BVMT Learning Trials (Immediate and Delayed Recall)			X			X		X
UMD Letter-Number Span			X			X		X
Trails A			X			X		X
TEPS-TRAIT			X			X		X
Category Fluency (Animals Only)			X			X		X

UPSA Brief			X			X		X
BIS/BAS			X			X		X
Faux Pas			X			X		X
Post Training Participant Survey[6]						X		
Post Training Clinician Survey						X		
Randomization			X					
Computerized training or treatment as usual[7]				X				
Telephone Check in[8]				X				

1: These visits can be broken up into 3-4 visits over 2-3 weeks as necessary to accommodate participant schedules. V3/V4 and V5/V6 can happen in either order, based on participant availability. If the visits

2: TCT/GCE participants will be encouraged to complete the training in 6 weeks if possible, but will be allowed up to 12 weeks to complete the 30 hours of training. All TAU participants will be followed for 12 weeks.

3: The SCID will only be conducted in complex cases when the MINI will not be sufficient to determine the participant's diagnosis

4: The review of medical records and medication lists will occur within +/-5 days of the scheduled visit.

5: Resource Utilization Survey will be captured at baseline, post-training, and 6-month follow-up. Study staff will use medical records, information from providers, and participant self-report.

6: If the participant disengages from clinical services and is unable to complete the post-training survey, study staff will complete the participant closeout report

7: Participants in the TCT/GCE arm will be asked to complete 5 60 minute sessions of cognitive training per week.

8: During the Intervention phase, the phone check in will be weekly for TCT and GCE participants to update them on training status. Participants randomized to TAU will not be contacted.

9: If there is a period of more than 2 weeks between the 2 appointments at each period (e.g., V1 & V2), the COVID19 Stress Screener will be re-administered at the second appointment.

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Appendix 1: Data Flow Chart