ANCILLARY REVIEWS

DO NOT DELETE. Submit the completed checklist below with your protocol.

Which ancillary reviews do I need and when do I need them? Refer to HRP-309 for more information about these ancillary reviews.			
Select yes or no	**Does your study…**	*If yes…*	***Impact on IRB Review***
☐ **Yes** ☒ **No**	Include Gillette resources, staff or locations	*Gillette Scientific review and Gillette Research Administration approval is required. Contact: research@gillettechildrens.com*	**Required prior to IRB submission**
☐ **Yes** ☒ **No**	Involve Epic, or Fairview patients, staff, locations, or resources?	*The Fairview ancillary review will be assigned to your study by IRB staff Contact:* ancillaryreview@Fairview.org	**Approval must be received prior to IRB committee / designated review.** **Consider seeking approval prior to IRB submission.**
☒ **Yes** ☐ **No**	Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection?	*The regulatory ancillary review will be assigned to your study by IRB staff Contact: medreq@umn.edu* *See: https://policy.umn.edu/research/indide*	
☐ **Yes** ☒ **No**	Require Scientific Review? Not sure? See guidance in the Investigator Manual (HRP-103).	*Documentation of scientific merit must be provided. Contact: hrpp@umn.edu*	
☐ **Yes** ☒ **No**	Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco?	*Complete the CPRC application process. Contact: ccprc@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam or brachytherapy)	*Complete the AURPC Human Use Application and follow instructions on the form for submission to the AURPC committee. Contact: barmstro@umn.edu*	**Approval from these committees must be received prior to IRB approval;** **These groups each have their own**
☐ **Yes** ☒ **No**	Use the Center for Magnetic Resonance Research (CMRR) or MR at Masonic Institute for the Developing Brain (MIDB) as a study location?	*Complete the CMRR pre-IRB ancillary review Contact: ande2445@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of recombinant or synthetic	*Complete the IBC application via eprotocol.umn.edu*	

	nucleic acids, toxins, or infectious agents?		**application process.**
☐ **Yes** ☒ **No**	Include the use of human fetal tissue, human embryos, or embryonic stem cells?	*Contact OBAO for submission instructions and guidance*	
☒ **Yes** ☐ **No**	Include PHI or are you requesting a HIPAA waiver?	*If yes, HIPCO will conduct a review of this protocol.* *Contact: privacy@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of a controlled substance?	*If yes, University Health and Safety Compliance for controlled substances will review the protocol.* *Contact:* cshelp@umn.edu	**Approval must be received prior to IRB approval.** **These groups do not have a separate application process but additional information from the study team may be required.**
☒ **Yes** ☐ **No**	Plan to use CTSI Monitoring services, and/or have an IND, IDE, or designated NSR-IDE by the UMN IRB?	*The CTSI monitoring ancillary review will be assigned to your study by IRB staff.* *Please note eligibility criteria* here. *Contact:* fencl003@umn.edu	
☐ **Yes** ☒ **No**	Use data from CTSI Best Practices Integrated Informatics Core (BPIC) Formerly the AHC Information Exchange (IE)?	*The Information Exchange ancillary review will be assigned to your study by IRB staff* *Contact:* bpic@umn.edu	
☐ **Yes** ☒ **No**	Use the Biorepository and Laboratory Services to collect tissue for research?	*The BLS ancillary review will be assigned to your study by IRB staff.* *Contact: Jenny Pham* *Pham0435@umn.edu*	
☐ **Yes** ☒ **No**	Have a PI or study team member with a conflict of interest?	*The CoI ancillary review will be assigned to your study by IRB staff* *Contact: becca002@umn.edu*	
☒ **Yes** ☐ **No**	Need to be registered on clinicaltrials.gov?	*If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff* *Contact:* fencl003@umn.edu	
☒ **Yes** ☐ **No**	Require registration in OnCore?	*If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff* *Contact: oncore@umn.edu*	**Does not affect IRB approval.**

PROTOCOL COVER PAGE

Protocol Title	Remote State Representation in Early Psychosis (Rem-STEP)
Principal Investigator/Faculty Advisor	Name: Caroline Demro, Ph.D.
	Affiliation: ☒UMN ☐ Fairview ☐ Gillette
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Scientific Assessment	Nationally-based, federal funding organizations
IND/IDE # (if applicable)	N/A
IND/IDE Holder	N/A
Sponsor-Investigator: Please check box	☒ This study will comply with ICH GCP requirements for drugs, biologics, and devices.
Investigational Drug Services # (if applicable)	N/A.
Version Number/Date:	Version: 11.0, Date: June 25, 2025

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
2.0	8.17.22	● Added ability to compensate participants for appointments going over allotted time ● Updated the "Resource Utilization" and MINI documents ● Added additional recruitment resource (BuildClinical)	No
3.0	09.30.2022	● Change PI to Melissa Fisher	Yes
4.0	02.15.2023	● Updated recruitment materials with new PI information ● Updated BuildClinical materials to better focus advertising. ● Adding the ability to combine RemSTEP NDA data with sister study, STEP. ● Updated participant payment and appointment time estimates ● Added new measures: 'Multidimensional Assessment of Interoceptive Awareness', SANS/SAPS, BPRS, GFR/GFS ● Lowered the maximum age of participants ● Clarified inclusion/exclusion criteria ● Added a follow up appointment	Yes

5.0	05.03.2023	● Updated age inclusion criteria to match consent form.	No
6.0	11.08.2023	● Transferred protocol from Advarra to UMN IRB ● Changed PI to Caroline Demro, Ph.D.	Yes
6.1	3.14.2024	● Responded to stipulations as follows: ○ Removed total compensation from recruitment materials. ○ Updated consent language to aid in comprehension ○ Updated consent form for consistency ○ Detailed emergency situation procedure in consent form	Yes
7.0	5.29.2024	● Replaced C-SSRS with screener version ● Added item asking about autism spectrum disorder in medical history form ● Replaced medication form with form that better captures medication information ● Added gender item to the screening form ● Added bonus for participants that complete the majority of cognitive training ● Added the ability to video record appointments to align with larger STEP study ● Added pre/post cognitive training surveys ● Added WHODAS	

		● Added IDI ● Changed the minimum hold length to 14 days to align with larger STEP study.	
7.1	6.27.2024	● Defined IDI in body of protocol ● Moved participant exclusion information from inclusion to exclusion section ● Clarified language on audio/video recording and storage ● Added page numbers to consent form ● Updated the participant interest form for clarity ● Moved the NDA information in the consent form to the risk section per HIPCO review ● Added optional item for use of future identifiable data in consent form	Yes
8.0	9.5.2024	● Increased participant recruitment goal ● Added healthy control participants ● Updated COPRR language in consent	Yes
8.1	10.31.2024	● Clarified discrepancies between payments by participant group ● Updated all materials to state that the study is completely remote	Yes
9.0	1.29.2025	● Made the following changes in response to QA Audit RNI00012052: ○ Added details on who is blinded. ○ Changed language surrounding	No

		condition assignment.	
9.1	2.18.2025	● Updated the following per IRB modification stipulations: ○ Crisis protocol information ○ Broken link to recruitment source ○ Randomization language	Yes
10.0	3.20.2025	● Removed the Follow Up appointment time point. ● Changed compensation and study duration to reflect the removal of Follow up time point.	Yes
11.0	6.20.2025	● Updated who the research is supported by including updating terms of certificate of confidentiality.	Yes

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ABBREVIATIONS/DEFINITIONS

- BPRS: Brief Psychiatric Rating Scale
- C-SSRS: Columbia Suicidality Severity Risk Scale
- CT: Cognitive Training
- DPX: Dot Pattern Expectancy Task
- GFS/GFR: Global Functioning Social/Global Functioning Role
- MAIA: Multidimensional Assessment of Interoceptive Awareness
- MINI: Mini International Neuropsychiatric Interview
- MNSS: Minnesota Symptom Severity Scale
- RCT: Randomized Controlled Trial
- SANS/SAPS: Scale for the Assessment of Negative Symptoms/Scale for the Assessment of Positive Symptoms
- TMB: Test My Brain
- UBACC: University of California San Diego Assessment of Capacity to Consent
- WHODAS: World Health Organization Disability Assessment
- IDI: Intersectional Discrimination Index
- COPRR: Consortium of Psychosis Research Registry
- EP: Early Psychosis
- HC: Healthy Control

1.0 Objectives

1.1 Purpose:

The purpose of the current study is to investigate computationally-informed precision treatments to improve two forms of state representation dysfunction observed in psychosis: 1) Abnormal perceptual inputs that impair state estimation; or, 2) Reduced state representation stability that affects cognitive control, working memory, and behavioral outputs. We will test the effects of two forms of cognitive training: visual perception training or visual cognitive control training in individuals with early psychosis. Participants will have the option to complete all training and assessments entirely remotely.

2.0 Background:

2.1 Significance of Research Question/Purpose:

Early psychosis can manifest low-level perceptual deficits (such as an abnormal mismatch negativity response); these perceptual abnormalities are observed in ~60% of individuals, where they are predictive of more severe disability at 12 month follow-up,[1] consistent with multiple studies showing that perceptual input abnormalities, when present, have a widespread deleterious downstream impact. Psychotic disorders can also manifest deficits in working memory, consistent with dysfunctional state representation stability, seen in ~80% of patients.[2] Thus, psychosis is heterogeneous in its underlying information processing pathology and clinical course, indicating a critical unmet need for precision treatment approaches.

We will address this unmet need by investigating the behavioral and neurophysiologic effects of a brief course of either visual perception training (designed to improve state estimation processes at the perceptual input level) or visual cognitive control training (designed to enhance state representation stability of visual information), in individuals with psychotic disorders such as schizophrenia, schizoaffective disorder, and bipolar disorder with psychosis. Because study visits may be conducted remotely, participants will be drawn from a national sample. Our goal is not to perform a treatment efficacy study comparing these two interventions. Rather, we seek to use predictions derived from basic and computational neuroscience to test the effects of neuroplasticity-based precision treatments targeting two distinct contributing information processing pathologies in psychosis, with the goal of improving state representation processes and cognition.

2.2 Preliminary Data:

We have extensive experience in the study of cognitive training for individuals with mental health conditions. We have completed 6 randomized controlled trials on the effects of cognitive and social cognitive training in individuals with psychosis,[3–7] including a large multi-site trial of cognitive training in recent-onset schizophrenia,[8,9] and in individuals at risk for psychosis.[10]

Cognitive training completed remotely in recent-onset schizophrenia and chronic schizophrenia.

We performed a double-blind randomized controlled trial (RCT) in 145 participants with recent-onset schizophrenia (mean age: 21 years).[8,9] Cognitive Training (CT) participants demonstrated significant improvements in global cognition, verbal learning and memory, and problem solving compared to computer games control participants. They also showed significant "target engagement"—gains in auditory processing speed-- that correlated with gains in global cognition (r = -0.47, p < 0.01). At a six month follow-up, participants in the active condition showed significant improvement in positive symptoms compared to controls, p = .045.

In a second multi-site, randomized controlled trial of cognitive training completed remotely, we tested the effects of social cognition training versus a computer games control condition in 108 individuals with schizophrenia.[6,11] Participants who completed the cognitive training condition showed improvements in social cognition, social functioning, functional capacity and motivation relative to the computer games control condition.

Remote recruitment, informed consent, assessments, and cognitive training in psychosis.

We also have extensive experience in conducting study procedures remotely. In an ongoing study of remotely provided cognitive training, participants are recruited across the U.S. and in 6 other countries and complete all study procedures remotely, including informed consent, clinical interviews, a cognitive assessment battery, and cognitive training (see ClinicalTrials.gov: NCT02782442). We are in the final year of this study and have enrolled 155 participants to date.

We have also completed several pilot studies on remotely delivered cognitive training,[12,13] remote assessments,[14] and a remotely delivered intervention designed to enhance motivation in individuals with psychosis.[15,16]

DPX and Bandit task variants:

We have examined state representation dysfunctions in psychosis from the perspective of state estimation and learning using a variant of the DPX task and a probabilistic reversal-learning variant of the Bandit task. These data converge in showing state estimation failures are common in patients with psychosis, whereas state learning deficits failures are rarer.

The DPX task variant consists of a series of pattern sequences. One pattern is designated the "A" cue, and another the "X" cue, which requires one response (AX, 60-70% of trials, e.g. respond left), while other sequences require a different response (AY or BX, 12-15% of trials each, or BY, 6-10% of trials, e.g. respond right). Given the strong expectation that X's engender a valid response, BX trials place

demands on the fidelity (stability, memory) of the "B" cue state representation to overcome this tendency. Many studies in our lab[17–21] and others' have shown patients with schizophrenia demonstrate specific deficits on the BX condition relative to controls, both in terms of d' measured as AX hits minus BX false alarms and a specific deficit on BX trials.

We have also examined a variant of the Bandit task that allows for the comparison of different failures in people with psychosis. This task uses choice options (neutral images) that are rewarded probabilistically (e.g., one image wins 80% of the time, the other 20% of the time). State learning associated with staying or switching stimuli too quickly (lose-switching) can be evaluated. The rewarded stimulus with the highest reward is changed over time. We have found that most people with psychotic disorders are relatively spared under these circumstances, with many showing failures in estimating the state, as shown by selecting the losing stimulus after winning on the correct stimulus.

2.3 Existing Literature:

A high degree of learning-dependent neuroplasticity is present even in patients who have been psychiatrically ill for years. Intensive training of perceptual processing and auditory/verbal working memory in adults with persistent schizophrenia generalizes to significant gains in untrained measures of cognition, is associated with enhanced quality of life up to 6 months after training, and "normalizes" MEG and fMRI brain activation patterns during perceptual processing as well as higher-order cognitive operations.[3,8,22,23] We have found similar behavioral gains in recent-onset schizophrenia, as well as training-related thalamic volume changes that are associated with improved cognition.[24] These emerging findings indicate that precision cognitive training methods that target the specific state representation dysfunctions of a given individual may lead to improved information processing that supports important clinical and functional gains.

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome:

Change in performance on novel variants of the DPX and Bandit tasks.

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s):

Change in performance on the Test My Brain cognitive battery, changes in symptom measures (SANS/SAPS, BRPS, GFR/GFS).

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

4.1 Description:

This study employs two computerized programs through Brain HQ, accessible on the web portal on the computer: a Visual Perception Training and a Visual Cognitive Control Training. Participants will be asked to use their assigned program for about 10 hours over the course of 4-6 weeks.

Several elements of flexibility are allowed in the schedule to accommodate the challenges that people with psychosis face:

- *Location of Use:* Participants will be encouraged to complete training from home or any other place that has access to a computer. Usage and progress tracking for both programs (treatment and control) is web-based and done online, allowing participants to complete training sessions on various computers, as convenient.
- *Extra Time:* To ensure a time-bounded study commitment, after 16 weeks such participants will perform their post-training assessment (completion) visits regardless of the number of training hours completed.
- *Variable Number of Total Sessions:* Given fatigue (common when using computerized cognitive training) and/or re-integration into work and home life, we expect that some participants will not be able to complete the desired ~5 hours per week, every week. To accommodate this, the coordinator will work out a schedule that is feasible, given the participant's life circumstances.
- *Cessation of Program Use While Continuing Participation in the Study:* In some cases a participant may wish to stop or minimize use of the program, while remaining in the study. Potential reasons for this decision might include a change in work circumstances, a change in residence, health issues, family/personal issues, or a lack of interest in program activities. While the participant will be encouraged to meet their personal commitment to scientific research, in such cases, after discussions with the Coordinator, the participant will be permitted to cease using the program and undergo the post-training assessment (completion).

Experimental Treatment Program (Cognitive Training)

The Experimental Treatment Program (Cognitive Training) is a computerized cognitive training program consisting of a set of specific cognitive exercises. To use the experimental treatment program, a participant opens a standard web browser on a broadband connected computer and goes to the experimental treatment program study web site. The participant then logs into the experimental treatment program server (using a study provided login that contains no personally identifiable information). The participant completes 30 minutes of scheduled cognitive exercises each day.

Participants perform tens to hundreds of trials over the course of a session, with auditory/visual feedback and rewards to indicate if the trial was performed correctly or incorrectly. After each session, the difficulty of the next session is updated to ensure that each participant is appropriately challenged. Summary screens including game metrics (points, levels) and exercise metrics (usage, progress) are shown to the participant at the end of each session.

All usage and progress data is encrypted then transmitted to a central server. In a research study such as this one, no personally identifiable information is stored on the BrainHQ server (including internet protocol addresses). The research coordinator will be able to log into the backend to check on the usage and progress for each active participant. This will be done to ensure that there is compliance, and to be able to customize their weekly phone/email/text check-ins. As well, this will be done to see if a training schedule should be made for the participant.

Below are descriptions of the specific cognitive training exercises in the treatment condition:

Visual Perception Training: Contains targeted visual perception exercises from BrainHQ's suite of cognitive exercises.

1. Visual Sweeps: Indicate the direction of two consecutive visual sweeps. Each gabor patch can sweep outward or inward.
2. Mind's Eye: A visual distractor suppression exercise requiring to choose the correct target within a pattern of distractors.
3. Hawk Eye: A speeded peripheral perception paradigm requiring the identification of target stimulus presented rapidly.
4. Divided Attention: A useful field of view speeded peripheral attention exercise requiring speeded responses to stimuli presented in the periphery.

Visual Cognitive Control Training: Contains targeted visual cognitive control exercises from BrainHQ's suite of exercises.

1. Mind Bender: A cognitive control task requiring speeded rule-guided responses.
2. Divided Attention: A speeded decision making exercise requiring attention to specific stimulus features while ignoring others.
3. Card Shark: A continuous performance working memory paradigm similar to a serial N-back task.
4. Freeze Frame: A response inhibition exercise requiring a suppression response to stimuli similar to the target.

4.2 Drug/Device Handling:

Study staff who are delegated the responsibility of assigning participants to their study intervention arm will create unique logins within the Posit Science training platform. Without this login information, access to the platform will not be available. The participants' usernames and passwords will be stored in a tracking log in Box to allow study staff to provide ongoing technical support to participants. In addition, staff will be able to monitor the participants' progress in the training platform from the back end of the Posit Science research portal; study staff will be able to see how

many blocks of training the participant has completed and which days the participant trained. Blinded study staff do not have access to the Posit Science research portal or the tracking log in Box.

4.3 Biosafety: N/A

4.4 Stem Cells: N/A

4.5 Fetal Tissue: N/A

5.0 Procedures Involved

5.1 Study Design:

The current study is a remotely delivered trial of two forms of cognitive training: visual perception training or visual cognitive control training. Study staff conducting analysis involving the training programs are blinded to training condition.

5.2 Study Procedures:

Intake: Participants will undergo consent procedures including a UBACC before being subject to a diagnostic assessment and a demographic questionnaire. Intake procedures will take place remotely via Zoom. Intake assessments will take approximately one hour to complete. For a list of Intake measures, please refer to Section 6.2 Data.

Baseline: If the participant passes the eligibility screen within the intake procedures, they may proceed to the Baseline Assessment Battery. Baseline procedures may be completed during the Intake appointment if the study team can verify eligibility. These assessments may also be completed remotely via Zoom. Baseline assessments will take approximately two hours for patients and 90 minutes for controls. For a list of measures completed in the Assessment Battery, please refer to Section 6.2 Data.

Training: Participants will be sequentially assigned 1:1 to twenty ~30 minute sessions of either Visual Perception Training or Visual Cognitive Control Training (described above). Training will be assigned to be completed over 2-3 weeks. During the training period, a member of the study team will be in regular contact with the participant (approximately once per week) to provide updates on their training progress. If a participant is not meeting the recommended schedule for training, the study team member may provide coaching and recommendations for how to improve adherence to the training protocol.

Post-Assessment: Upon completion of the training program, or after 16 weeks have passed, the participant will be asked to complete the self-administered Assessment Battery, which may be completed remotely. The appointment will last approximately

two hours for patients and 90 minutes for controls. For a list of measures completed in the Assessment Battery, please refer to Section 6.2 Data.

Video or Audio Recording: If participants provide their consent for the diagnostic and clinical interviews to be videotaped or audio recorded, Zoom will be used, and the video or audio-only file will be saved. Please refer to Section 6.0 Data Banking for clarification on how video data will be stored.

5.3 Study Duration:

Anticipated study duration will be approximately 2 months, though participants can remain enrolled for up to 8 months to complete all study activities (as post-assessments may occur up to 16 weeks after training assignments).

5.4 Use of radiation: N/A

5.5 Use of Center for Magnetic Resonance Research: N/A

6.0 Data and Specimen Banking

6.1 Storage and Access:

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

As this study is a component of the “Dysfunctional State Representations in Psychosis” grant awarded to Dr. Vinogradov, the de-identified data from this study will be merged with the data from a sister protocol, “State Representation in Early Psychosis (STEP)”, STUDY00009964 in a master dataset. These studies use similar assessment batteries and training paradigms, and their data will be analyzed together. This master dataset will be stored on Box.

For a visual representation of the flow of study data, please refer to **Appendix 2 Data Flow Diagram.**

Consent Documents: Consent documents will be collected in REDCap or on paper. Consents that are collected on paper will be stored in locked cabinets in locked offices. These documents will be scanned into a dedicated folder within Box or REDCap. Consent documents will not reside in the same REDCap database or paper binder as de-identified participant data to keep PHI separated. These records will be made available to any reviewing body, but will not be shared with any collaborators.

Computerized Tasks: The DPX and Bandit task variants will be completed via the web-based data acquisition tool developed by LATIS/HST and will be stored in a University-managed data storage platform for data analysis. When extracted into the storage platform, data will contain the date and time of collection; no other direct identifiers are collected with the tasks. These computerized tasks may also be collected on a LATIS- or HST-supported device through a presentation software (E-Prime, PsychoPy, etc.) if needed – for example, if the LATIS/HST Managed Database Server is down or under repair.

Assessment Data: The cognitive assessment data (TMB) will be collected using outside applications and will be stored on secure servers hosted by the Many Brains Project. These data will not contain personally identifying information, but will use the subject's unique identifier to collate assessment data. The University of Minnesota has entered into a DUA with the Many Brains Project; these records are maintained by study staff. No direct identifiers will be collected. TMB data will be made available to the research staff through the back-end of the website; staff will copy the outcome data manually into a University-managed data storage platform. The Many Brains Project will maintain their own copies of the data collected during this trial and reserve rights to use the data for their own purposes as per the data sharing agreement.

Clinical assessment data (MNSS, C-SSRS, SANS/SAPS, BPRS, GFR/GFS) and participant history information (demographics, medical history, medication list, treatment history, resource utilization, MAIA) may be collected in REDCap or via paper or pdf forms. The diagnostic interview (MINI 7) may be collected on paper or PDF, and a PDF will be uploaded to REDCap or Box. Paper or PDF forms will be entered into REDCap or the University-managed Database Server using HST- or LATIS-supported devices. The paper or pdf forms will be scanned and retained in Box Secure Storage or REDCap. Scanned paper forms will be checked for completion and legibility, and any paper copies will be shredded; they will be kept in locked cabinets in locked offices until they can be shredded.

Training Data: Cognitive training data will be collected through a web browser or 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. 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 data from the BrainHQ website and store this data in a University-managed Database Server. Access to files containing training condition assignments is limited to staff not blinded to condition.

Video or Audio Data: Video/audio data will be recorded via Zoom using HST- or LATIS-supported devices for remote visits. Participants will be asked in the consent form if they would agree to video/audio recording and for what purpose(s). The appointment will only be recorded if the participant agrees to the recording. After the assessment appointment is complete, a member of the study staff will upload the file into a secure folder within Box. Study staff will record the data to their local HST- or LATIS-supported device. Once the study staff has confirmed that the file has successfully uploaded to Box the video/audio file will be erased from the recording device. In the case that a video/audio file needs to be downloaded off of Box for viewing it will be stored on an HST- or LATIS-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: An enrollment log containing the participants' personally identifying information, such as name and contact information, will be stored in Box or REDCap. Additional tracking data may be stored on additional spreadsheets in Box or REDCap. Only qualified study staff will have access to the study folder.

A Participant Consent database will be maintained in REDCap until six years after the study's completion. Access to these servers will be limited to qualified study staff listed on the delegation of authority log. Access will not be given to collaborators who wish to use the database for research projects.

6.2 Data:

- Screening and Intake Battery:
    - Demographics Questionnaire
    - Medical History
    - Medication List
    - Treatment History and Resource Utilization (EP only)
    - Abbreviated Mini International Neuropsychiatric Interview (MINI-7). Only the following modules will be completed:
        - Depression

        - Mania
        - Substance Use
        - Alcohol Use
        - Psychosis
    - Columbia Suicide Severity Rating Scale (C-SSRS)
- Assessment Battery:
    - DPX task variant
    - Bandit task variant
    - Test My Brain Battery (TMB)
    - Minnesota Symptom Severity Scale (MNSS)
    - Multidimensional Assessment of Interoceptive Awareness (MAIA)
    - WHODAS: This 12-item measure assesses six domains of functioning including cognition, mobility, self-care, social interaction, and social and participatory activities.
    - Intersectional Discrimination Index (IDI): This 31-item measure assesses anticipated, day to day, and major discrimination experienced by the participant.
    - Sound Sweeps (Posit Assessment)
    - Syllable Stacks (Posit Assessment)
    - SANS/SAPS: The SANS (25 items) and SAPS (34 items) assess negative and positive symptoms of schizophrenia. (EP only)
    - BPRS: This 24-item scale assesses psychiatric symptoms.
    - GFS/GFR: These scales provide a rating on a scale from 1-10 for social functioning and for role functioning.
    - Pre cognitive training survey: 14-item survey to assess subjective view of cognitive training prior to starting training (completed only at Baseline)
    - Post cognitive training survey: 19-item survey to assess subjective view of cognitive training after finishing training (completed only at Post-Assessment)
- Training Data:
    - BrainHQ visual perception and visual cognitive control exercises

6.3 Release/Sharing:

Please see Section 6.1 for data sharing with the Many Brains Project and Posit Science. No direct identifiers will be shared and there will be appropriate data sharing agreements in place between the University of Minnesota and these entities.

Data from this study will also be shared with the NIMH Data Archive National Database for Clinical Trials related to Mental Illness (NDCT). This system will allow researchers from other institutions to access the data, after completing the necessary agreements with the NIH. Participants are asked in the Consent Form if they consent to data being shared with the NIMH data archive. The data that will be shared will be collated under a unique identifier, known as a GUID (Global Unique Identifier). The data will be de-identified with the exception of age in time of months and date of

assessment. The data will be combined with this study's larger counterpart study, "State Representation in Early Psychosis (STEP)", STUDY00009964, prior to being uploaded to the NDA.

7.0 Sharing of Results with Participants

7.1 Sharing Results:

Individual results from any training, ratings, or assessments will not be shared with the participant.

7.2 Sharing Genetic Results:

7.2.1 Disclosure of Results: N/A

7.2.2 Returning Results to Participants: N/A

7.2.3 Future Analysis of genotypes: N/A

8.0 Study Population

8.1 Inclusion Criteria:

All Participants:

- Between the age of majority and 30 at the time of enrollment
  - Alabama: Age 19-30
  - Nebraska: Age 19-30
  - Mississippi: Age 21-30
  - All other states: 18-30
- Fluent in spoken and written English, in that the participant learned to speak English before the age of 12 or is able to demonstrate fluency in conversation with study staff
- Has an outpatient status and no hospitalization of at least 1 month prior to participation
- Has access to a computer with internet connection
- United States address as permanent residence
- Estimated IQ at or above 70, as estimated by the cognitive assessments

Early Psychosis Participants:

- MINI confirmed clinical diagnosis of the following: schizophrenia, schizoaffective disorder, schizophreniform disorder, psychosis NOS, major depressive disorder with psychotic features, or bipolar disorder with psychotic features.
- Willing to share contact information for a clinical provider

8.2 Exclusion Criteria:

All Participants:

- We will exclude participants with a history of severe substance use in the past 3 months, as determined by the PI/Co-Is. Participants will be excluded if there is concern about their ability to remain sober during assessments and training.
- Subject is unable to demonstrate adequate decisional capacity, in the judgment of the consenting study staff member, to make a choice about participating in the research study
- The presence of a neurological disorder that, in the opinion of the PI/Co-Is, would impede participation in the study or would put the participant at additional risk by participating
- Previous clinically significant head injury or prolonged unconsciousness, as determined by the PI/Co-Is
- Significant cognitive training experience within the past 6 months, as determined by the PI
- Meets criteria for clinical risk of suicidal behavior, as defined by:
  - Clinician judgment
  - A suicide attempt within 3 months of enrollment
  - Active suicidal ideation at screening or baseline, as indicated by the C-SSRS
  - Previous intent to act on suicidal ideation with a specific plan and/or preparatory acts within 3 months of enrollment, as indicated by the C-SSRS
- Anyone who does not meet the aforementioned criteria

Healthy Control Participants:

- Meets DSM-5 criteria for psychotic, bipolar, or autism spectrum disorder
- Has a family history (1st degree relative) of psychotic, bipolar, or autism spectrum disorder

8.3 Screening:

Individuals who self-identify or are referred to the study will be provided with a brief introduction to the study by the study coordinator, who will then ask if the person is interested in participating. If the person says yes, the study coordinator will conduct a phone screen to determine the individual's eligibility to participate. People who pass the phone screen will then be invited to participate in a consent discussion and enroll in the study.

9.0 Vulnerable Populations

9.1 Vulnerable Populations:

Population / Group	Identify whether any of the following populations will be focus of the research (targeted), included, but not necessarily the focus or excluded from participation in the study.
Children	Excluded
Pregnant women/fetuses/neonates	included but not the focus
Prisoners	Excluded.
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	Primary focus of the research
Non-English speakers	Excluded
Those unable to read (illiterate)	Excluded
Employees of the researcher	Excluded
Students of the researcher	Excluded
Undervalued or disenfranchised social group	included but not the focus.
Active members of the military (service members), DoD personnel (including civilian employees)	included but not the focus.
Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.	Excluded

Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare.	included but not the focus
Individual or group with a serious health condition for which there are no satisfactory standard treatments.	included but not the focus
Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior).	included but not the focus
Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research.	included but not the focus.

9.2 Additional Safeguards, if any, to ensure inclusion is appropriate:

As this is a minimal risk study, vulnerable populations such as pregnant women, active members of the military, individuals with serious health conditions without satisfactory treatments, disenfranchised social groups, disadvantaged individuals, and individuals with concerns of negative consequences for not participating in research will not face any additional risk by participating in this study.

Some participants in this study will be diagnosed with a psychotic illness, which could result in fluctuating capacity to consent to research. All participants will need to pass assessment with the UBACC in order to enroll in the study. Participants will not be approached for participation in the trial during times of clinical instability, such as during hospitalization. Please refer to section 12.2 Withdrawal Procedures, Section 18.2 Data Safety Monitoring, and Section 21.6 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent for further information about how fluctuations in capacity to consent will be approached during this study.

As Investigators in this protocol are also clinicians who treat individuals with psychosis, it is possible that some of their patients may be recruited for this study. In order to prevent therapeutic misconception, Investigators will follow a script that explains their dual roles in the clinic and in the research, and will inform participants which activities are considered part of their regular care and which are considered optional research activities prior to initiation. Patients will be reminded that they do

not have to complete research activities and that their choices will not impact their clinical care. If a patient is interested in research, the Investigator will introduce them to a member of the study team; Investigators will not be directly involved with consent of their own patients.

Non-English speaking individuals will not be recruited for this study, as the standardized interviews, computerized tests, and cognitive training are only available in English and cannot be reasonably translated. Similarly, illiterate individuals will not be enrolled as the study tasks require reading instructions and responding to self-report questionnaires independently.

9.3 If research includes potential for direct benefit to participants, provide rational for any exclusions indicated in the table above:
N/A

10.0 Local Number of Participants

10.1 Local Number of Participants to be Consented:
We seek to consent and enroll up to 150 early psychosis participants and up to 50 healthy control participants.

11.0 Local Recruitment Methods

11.1 Recruitment Process:

We will recruit participants remotely via ads on websites such as Craigslist, Reddit, schizophrenia.com, and NAMI in cities all across the U.S. Additionally, this study will be advertised on the Department of Psychiatry's website, clinicaltrials.gov, studyfinder.umn.edu, and Dr. Vinogradov's personal research websites. Other websites with the intent of recruiting individuals for research or providing news and opportunities to individuals with psychosis may be approached for advertisement for this study.

In addition, participants who were screened for a different study at UMN and who have consented to be contacted for future research studies may be contacted by the research coordinator.

We will utilize the Consortium of Psychosis Research Recruitment (COPRR) in the Department of Psychiatry & Behavioral Sciences and the Department of Psychology. 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 Honest Broker 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.

We will additionally utilize BuildClinical, a vendor for social media advertising. BuildClinical is a data driven software platform that helps academic researchers recruit participants for research studies more efficiently using social media, software, and machine learning. They have worked with IRBs in the US to ensure they adhere to all the appropriate guidelines and procedures. They utilize study-specific advertisements to engage participants on digital platforms such as Facebook, Google, WebMD, etc. and redirect them to a study-specific landing page should they click it. On the landing page, the person can complete an online pre-screen questionnaire that gets routed into BuildClinical's platform. Study staff will then be given the results of the questionnaire. BuildClinical's Secure Socket Layer (SSL) software, which encrypts all inputted information, keeps information private and HIPAA compliant. BuildClinical's backend servers are stored in the USA at some of the most secure data centers in the world.

The outpatient Psychiatry Clinic in the Department of Psychiatry at the University of Minnesota provides new patients the opportunity to indicate whether they are interested in being contacted to hear about research studies or whether they prefer to not be contacted. Access to this contact information is managed by the Department of Psychiatry Clinical Research Advocate. The Clinical Research Advocate describes research opportunities to patients and provides the contact information of interested patients to departmental researchers conducting studies for which they might be eligible. We are requesting permission to receive this contact information to recruit participants for this study. We will only contact patients who have indicated an interest in hearing about research.

This study will also be advertised at community events (e.g., conferences) and locations (e.g., community support programs) using flyers and/or brochures. A flyer will be posted at the Psychiatry Outpatient Clinic and Mental Health Neuromodulation Clinic bulletin boards, and the study may be advertised on TVs within the clinics. We will post flyers/brochures in community mental health groups that are interested in learning about the research study.

11.2 Identification of Potential Participants:

Most participants in this study will self-identify to recruitment materials. Some will be identified through recruitment registries or referrals. Private records will not be used to identify potential participants. Initial contact will be made by either the study coordinator or the Department of Psychiatry Research Advocate. These individuals will provide interested parties with information about the study and if the person is interested, begin screening procedures.

11.3 Recruitment Materials:

- Online posting/advertisement (e.g., craigslist, Reddit)
- Tear-away flyers, brochures, business cards
- NAVIGATE Program newsletter
- Community mental health clinics
- Websites, including:

- https://med.umn.edu/psychiatry/research
- http://vinogradovlab.umn.edu/current-studies
- Clinicaltrials.gov
- Researchmatch.org

11.4 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 cognitive 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.

- Intake: $25
- Baseline:
  - EP Participants: $50
  - HC Participants: $40
- Training: $15 per hour x 10 hours = $150
- Bonus for completing 220/240 levels of training or more = $50
- Post-Assessment:
  - EP Participants: $50 + $25 bonus
  - HC Participants: $40 + $25 bonus
  -
- Total compensation:
  - EP Participants: $350
  - HC Participants: $330

In addition, participants may earn up to $30 for completion of the DPX and Bandit task variants at Baseline, Post-Assessment, and Follow-up ($60 total). In sum, early psychosis participants may earn up to a total of $410, and healthy controls may earn up to a total of $390.

If study appointments go over the allotted time, study staff can compensate participants for the additional time. Participants will be compensated at a rate of $20/hour, rounded up in 15 minute increments.

Participants may request to receive their payments in installments rather than as a “lump sum” after 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 $20/hour, rounded up in 15 minute increments.

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

12.0 Withdrawal of Participants

12.1 Hold Procedures:

Participants' engagement in the study will be postponed if they are hospitalized for psychiatric reasons during the study or if they become actively suicidal during the study. The hold period will last a minimum of fourteen days. A study team member will follow up on the improvements of the participants' condition. Once the participant's condition is stable, the study staff member may request to schedule a time to re-perform the UBACC for the participant to continue with the study. If a participant's engagement is postponed for longer than six months, the clinical determination to withdraw the participant from the study is individually reviewed by the PI. If the PI determines to withdraw the participant from the study due to worsening psychiatric symptoms over an extended length of time, they may rejoin the study, if they wish, when their condition has improved.

12.2 Withdrawal Circumstances:

Participants who choose to withdraw from the cognitive training portion of the study may be asked if they are willing to complete interview appointments at the Post-Intervention point. If a participant agrees, they will no longer be asked to participate in the cognitive training program.

A participant may choose to withdraw from the study at any time, for any reason. Their decision to withdraw from the study will not impact their normal care or their relationship with the University of Minnesota.

12.3 Withdrawal Procedures:

Participants may withdraw from the study before completing study procedures. Study staff will not continue to collect any data after a participant withdraws. Data already collected from these participants will not be removed from the database.

12.4 Termination Procedures:

Throughout the course of the study, if a participant meets one or more of the following criteria, the PI may choose to terminate the participant's involvement without their consent. The criteria are as follows:

- The participant is incarcerated
- As a result of worsening psychiatric symptoms, the participant had been placed on hold from continuing study tasks for a period of six months or more
- The participant suffers from a serious illness or injury (such as a traumatic brain injury) that permanently affects their ability to provide informed consent or participate in study activities, in the judgment of the Investigators
- A clinical determination, by the Investigators, that continuation in this study is not in the participant's best interest
- The participant cannot be reached to schedule follow up appointments after a minimum of three attempts by study staff
- The participant repeatedly misses scheduled appointments without notifying study staff prior to the appointment time

When the PI has made the determination to withdraw a participant without their consent, data will no longer be collected from that participant. All of the data that had been collected prior to the participant's withdrawal will remain in the database. Data, such as participant's full name and signed consent form, will reside in our database to provide validation that the participant had consented to partake in this study prior to withdrawal.

13.0 Risks to Participants

13.1 Foreseeable Risks:

Though this is a minimal risk trial, we will conservatively follow guidelines for medical devices (i.e., computerized cognitive training) in the reporting of adverse events in this trial, which defines unanticipated adverse device effects (UADEs) in The Code of Federal Regulations in 21 CFR 812.3(s) as any serious adverse effect on health or safety associated with a device. The PI will assess all adverse effects for their severity, their unexpectedness, their relation to study procedures, and whether they represent increased risk to other participants or the greater community. The PI will report adverse events to the IRB as required by HRP-103 Investigator Manual.

All risks will be explained in detail in the consent documents so participants can make an informed decision about enrolling in this trial.

Privacy and Confidentiality: Participation in research may result in a loss of privacy due to the data collected during study activities, if the data is mismanaged. Records will be handled as confidentially as possible.

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 must opt in to email communication in this study to complete remote study activities. Participants will be able to enroll in ProofPoint secure email, or they may sign an Unsecure Email Authorization form for regular email communication. If they change their mind about communicating via email, they can notify staff at any time about their communication preferences.

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.

Assessment Risks: The potential risks of this project include those associated with routine clinical interviews. The clinical interview instruments to be used for the project could induce boredom and fatigue. However, breaks in interview sessions will be given whenever the subject requests or when obvious fatigue is observed. At times participants may be uncomfortable with the questioning as some questions are sensitive in nature. There are no known risks associated with any of the cognitive testing procedures to be used in the proposed project. There are no alternative procedures or methods available with less risk or cost that provide comparable information to that obtained by the procedures described in this proposal.

Cognitive Training Risks: Though the cognitive training platform is well tolerated by a wide range of individuals, some participants report boredom, frustration, or fatigue.

13.2 Reproduction Risks: N/A

13.3 Risks to Others: N/A

14.0 Potential Benefits to Participants

14.1 Potential Benefits:

There are no direct benefits to participants. Participants who receive cognitive training may notice changes to their thinking and problem solving skills. Information that participants provide will help healthcare professionals better understand new ways to treat psychosis in the future. This study is not a substitute for therapy, and participants will continue seeing their mental health care practitioners.

15.0 Statistical Considerations

15.1 Data Analysis Plan:

We will examine change in the DPX and Bandit task variants (specifically by examining parameter changes in the fit attractor dynamic models), TMB Cognitive Battery performance, and symptom and functioning measures from pre-intervention to post-intervention. Data collected under this protocol will be analyzed with data from the data collected in the sister study, “State Representation in Early Psychosis (STEP),” STUDY00009964.

15.2 Power Analysis:

- *Visual Perception Training:* The following power analysis is based on the effect size of distractor suppression change from 6 hours of auditory perception/discrimination training in older adults (*N*=16, *d*=1.00, Mishra et al., 2014). With 40 participants, and a conservative attrition rate estimate of 25%, power is estimated at 99% to detect changes in distractor suppression at alpha level=.05, two-tailed test.

- *Visual Cognitive Control Training:* The following power analysis is based on the effect size of theta power change from 10 hours of working memory and executive functioning training in outpatients with schizophrenia spectrum disorders (*N*=35, *d*=1.01, Best et al., 2019). With 40 participants, and a conservative attrition rate estimate of 25%, power is estimated at 99% to detect changes in theta power at alpha level=.05, two-tailed test.

15.3 Statistical Analysis:

We will conduct an intent- to-treat analysis using linear mixed-effects models, with group and time as fixed factors. Model parameters will be estimated using restricted maximum likelihood. Since this is not an efficacy trial, we will also conduct a per-protocol analysis on study completers using repeated measures ANOVA. As an additional part of this study, we will also be able to examine target engagement of the visual perception and cognitive control respectively over the course of training. We will use locally weighted regression analysis (lowess) to characterize the relationship between visual perception/cognitive control and time non-parametrically. We will then compare group trajectories using mixed model analysis.

15.4 Data Integrity:

Virtually all data collected as part of this study will be collected through, or entered into, established digital platforms. These methods greatly reduce the chance of error in data collection and scoring that comes with manual methods.

The study team will use the services of HST and LATIS to manage and supervise data collection and storage in this project. Their teams will set-up the infrastructure to merge and combine data from this project into a UMN-managed data storage platform. This system will undergo regular updates throughout the course of the proposed project. To verify the integrity of the data, the tool will undergo systematic checks to ensure the existing data collection streams are not altered before the updates are completed. Any changes in this environment will leave the original data unaffected. In some cases, the research staff may be granted permission to extract de-identified data from the data shelter for analysis if the processing power of the data shelter is not sufficient for the task at hand.

16.0 Health Information and Privacy Compliance

16.1 Select which of the following is applicable to your research:

☐ My research does not require access to individual health information and therefore assert HIPAA does not apply.

☒ I am requesting that all research participants sign a HIPCO approved HIPAA Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

☐ I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

Appropriate Use for Research:

☐ An external IRB (e.g. Advarra) is reviewing and we are requesting use of the authorization language embedded in the template consent form in lieu of the U of M stand-alone HIPAA Authorization. Note: External IRB must be serving as the privacy board for this option.

16.2 Identify the source of Private Health Information you will be using for your research (check all that apply):

☐ I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me

☒ I will collect information directly from research participants.

☐ I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

☐ I will pull records directly from EPIC.

☐ I will retrieve record directly from axiUm / MiPACS

☐ I will receive data from the Center for Medicare/Medicaid Services

☐ I will receive a limited data set from another institution.

☐ Other. Describe:

16.3 Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed: N/A

16.4 Approximate number of records required for review: N/A

16.5 Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes:

☐ This research involves record review only. There will be no communication with research participants.

☐ Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.

☒ Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants.

Participants may be contacted by study staff by phone, email, or text. If opting to use email, participants will be asked to sign an Unsecure Email Authorization Form or to

create an account with ProofPoint. Similarly, participants opting to use texting will be asked to sign the Texting Authorization Form.

16.6 Explain how the research team has legitimate access to patients/potential participants:

Participants will either self-identify to this study, or be referred to us through community partners. Referring sources will obtain verbal permission to share potential participant contact information with the study team.

17.0 Health Science Technology (HST) HIPAA Compliant Devices and Data Storage

17.1 HST Device Number:

20202003; 20191358; 20191359; 20230569; 20220915; 20191143; 20232137; 20221791; 20191860; 20221646

Other non-HST managed devices: N/A

17.2 Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply):

☒ In the data shelter of the Information Exchange (IE)

☒ Store ☒ Analyze ☒ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store ☐ Analyze ☐ Share

☒ In REDCap (recap.ahc.umn.edu)

☒ Store ☒ Analyze ☒ Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

☐ In OnCore (oncore.umn.edu)

☐ Store ☐ Analyze ☐ Share

☒ In the University's Box Secure Storage (box.umn.edu)

☒ Store ☒ Analyze ☒ Share

☐ In Advarra EDC

☐ Store ☐ Analyze ☐ Share

☐ In UMP devices/servers

☐ Store ☐ Analyze ☐ Share

☐ In Fairview devices/servers

☐ Store ☐ Analyze ☐ Share

☒ In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

Server: prodphr.ahc.umn.edu

Contact: Jordan Bell bellx445@umn.edu

☒ Store ☒ Analyze ☒ Share

☒ In an AHC-IS supported desktop or laptop.

Provide UMN device numbers of all devices: See Section 17.1

☒ Store ☒ Analyze ☐ Share

☐ Other. Describe:

Indicate if data will be collected, downloaded, accessed, shared or stored using a server, desktop, laptop, external drive or mobile device (including a tablet computer such as an iPad or a smartform (iPhone or Android devices) that you have not already identified in the preceding questions.

☐ I will use a server not previously listed to collect/download research data

☐ I will use a desktop or laptop not previously listed

☐ I will use an external hard drive or USB drive ("flash" or "thumb" drives) not previously listed

☒I will use a mobile device such as an tablet or smartphone not previously listed

Study staff will use University-owned smart phones to communicate with participants.

17.3 Consultants. Vendors. Third Parties:

The neurocognitive battery (TMB) will be collected with a third party platform (the Many Brains Project). These data will be stored on secure servers hosted by the owners of the application. Cognitive training data will be collected through the BrainHQ web browser or iOS app and stored on secure servers hosted by Posit Science. Adequate Data Sharing Agreements (as determined by HIPCO) will be maintained between the University of Minnesota and these 3 entities. Please see Section 6.0 Data Specimen and Banking and Section 6.3 Release/Sharing for additional details.

17.4 Data Ownership:

☒ UMN
☐ UMP
☐ Fairview
☐ Sponsor:
☐ Third-party university:

☐ Other (specify):

17.5 Links to identifiable data:
A unique study identification code will be linked to the participant's identity. This information will be kept separately in an enrollment log housed in Box or REDCap, and will be destroyed six years after the study's completion.

17.6 Sharing of Data with Research Team Members:
Data will be shared via Box and via the LATIS/HST Managed Database Servers.

17.7 Storage of Documents:
Data in this study will be collected primarily in digital format. Any paper records will be kept in locked cabinets of the locked offices of study team members. Paper records of data and consent forms will be scanned into Box Secure Storage or REDCap. This information will be retained in Box for a minimum of 6 years after the completion of the study.

17.8 Disposal of Documents:
After confirming the scanned copy is complete and legible, study staff may shred the paper copy of these records to protect confidentiality.

18.0 Confidentiality

18.1 Data Security:
University of Minnesota study staff will complete GCP, CITI, HIPAA and 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 study data will be kept on password-protected, HIPAA compliant, secure servers.

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 unless required by law. Study staff will only be provided with access to the study data that they need to perform their work duties.

The University of Minnesota will maintain appropriate data sharing agreements with the Many Brains Project and Posit Science. This study has a Certificate of Confidentiality issued by the NIH. The Certificate of Confidentiality only covers data that was collected under the original NIH-supported grant. This grant ended on 5/31/2025. Any data that is collected after this date will not be covered by a Certificate of Confidentiality.

A copy of the consent form or other research study information will not be placed in the participants' medical, employment, or educational records.

For a description of how data is collected, stored, and shared, including whether direct identifiers or other PHI are included in the data sets, please refer to Section 6.0 Data Banking and Appendix Data Flow.

18.2 Data Sharing:

By design, data collected within this study will not contain direct identifiers. Data that is shared with collaborators, including with the NDA, will include the original date of data collection.

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

19.1 Data Integrity Monitoring:

The PI's will meet weekly and will oversee the progress of the study. Data specialists from LATIS/HST will ensure there are secure methods in place of obtaining and handling participant data. All regulatory and subject 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.

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 team members 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 team members will be trained by the investigators to recognize symptoms that indicate worsening clinical status, suicidal and homicidal ideation, self-harm, and abuse or neglect.

Study team members will deliver regular participant updates to the PI and Co-Is at the Neuro-PRSMH P50 Study Meeting and other team meetings. In the case where a Study team member misses a team meeting, they will coordinate with their supervisor or an Investigator to deliver participant updates.

If a study team member 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 Vinogradov Lab 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. The Vinogradov Lab Crisis Protocol is a living document and will be maintained on the CoTIPP Lab Google Drive at the following path location: CoTIPP Lab Research Drive > 1. Crisis Plans > 1. Vinogradov Lab Crisis Protocol. The document can be accessed by lab personnel at z.umn.edu/cotipp_crisis.

If a study team member learns of a mandated reporting scenario, such as 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. A PI will determine whether the event needs to be reported to the IRB, per HRP-103 Investigator Manual.

Protocol Specific Conditions

Anticipated Adverse Events: As this study enrolls participants with a psychotic illness, worsening psychiatric symptoms, suicidality, and associated hospitalizations are known risks of the population, and thus will not meet prompt reporting requirements to the IRB, per 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 asked to provide contact information for a clinical provider. These individuals will only be contacted in circumstances in which the study team learns of a concerning change in mental health status, or the participant indicates harmful intentions towards themselves or others. As this is a remote study, provider contact information is required to participate.

Participants will also be asked to provide contact information for an emergency contact, which can be a family member or friend. Study staff may contact this person if there are concerns for a participant's well-being (following the Crisis Protocol).

Research staff will not share details of the individual's study participation with others unless they have written authorization from the participant directly (such as an email).

To protect the participant's privacy, we will only store data with no direct identifiers within our databases. Personally identifying information such as name, contact information, and date of birth will also be stored in the Enrollment Log. This information will be destroyed six years after the study's completion. The date that a participant completes the study assessments will be collected and stored alongside their other study data.

Some participants may be asked to allow a research staff trainee to sit in on their consent appointments and/or follow-up appointments. If the participant does not agree, the trainee will not be invited in the room to observe the appointment. Similarly, the participant may choose to have a guest sitting in on their appointment with them.

Participants may opt to use email communication with study staff to arrange for appointments and send other study instructions. Participants may choose between using encrypted emails (Proofpoint) or unencrypted emails. If participants opt in to receive unencrypted emails from study staff, they will be asked to sign the Unsecure Email Authorization form. Similarly, participants may opt into using text communication with a University-owned cell phone.

Participants will be reminded during interview sessions that their participation in this study is completely voluntary, which means that they do not need to complete any activities that make them feel uncomfortable or stressed. They will be instructed to inform the study team member if they would like to decline to do any task or set of tasks, postpone procedures, or withdraw from the study entirely. Participants will also be encouraged to take breaks as needed during appointments.

20.2 Access to Participants: N/A

21.0 Compensation for Research-Related Injury

21.1 Compensation for Research-Related Injury: N/A

21.2 Contract Language: N/A

22.0 Consent Process

22.1 Consent Process (when consent will be obtained):

As much as is possible, participants will be provided a copy of the Combined HIPAA Authorization and Consent Form and other consent documents in advance (e.g., via email) to allow them to review the documents prior to the consent appointment.

Consenting will be conducted remotely over Zoom or by phone. 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 participant. After explaining the study, the participant will be allowed as much time as needed to review the consent documents and ask questions before making the decision to participate. The participant can delay enrollment and return to sign the consent forms at a later time.

After the study team member has described the study, all participants will be assessed for comprehension of study procedures using a modified version of the UBACC. 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. While the UBACC is also used to assess capacity to consent, it is a brief, structured form which accomplishes the teach-back method of consent. Participants must score a 75% or higher (14/18) on the UBACC in order to be allowed to consent. 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.

Consenting procedures will comply with the University of Minnesota's Part 11 compliant e-Consent procedures. Participants will be provided a link to the REDCap consent database via email prior to their appointment. In order to confirm the participant is signing the consent form at the appropriate time, the consent form will require a unique code to be entered into REDCap; without this code, the REDCap survey will not open and the participant will not be able to complete the consent document. At the end of the form, participants will be able to sign the document using a mouse, trackpad, or touchscreen. The study team member will also sign and date a separate form to indicate their participation in the consent process. Participants will be provided with a copy of the e-consent forms after the forms have been signed via automatic emails from the REDCap platform.

In addition to the primary Combined HIPAA Authorization and Consent Form, participants will be asked to sign Unsecure Email and/or Texting Authorization Forms, should they opt in to using these methods of communication.

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

22.3 Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained):

Prior to conducting the screening questionnaire, potential participants will be asked whether the study team can ask them some questions to determine if they may qualify for the study. Only verbal consent will be obtained at this stage. Individuals

who participate in the phone screen will be asked if study staff may keep their information to contact them again 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 may be maintained in paper format (in locked cabinets in locked offices) and scanned into Box, or collected in REDCap.

Similarly, potential participants may also complete a screening questionnaire independently on REDCap. These individuals will be informed that this information will be saved in REDCap, and will involve storing their name and contact information. Participants will be asked whether this information could be used to contact them for other research opportunities in the future. The REDCap screening questionnaire will not contain all of the elements of informed consent, and participants will not sign the form; rather, they will select a radio button which states "I agree to answer some questions about my health history and to provide contact information so that the study team can contact me about this study." They will select this button prior to beginning the REDCap questionnaire.

22.4 Non-English Speaking Participants: N/A

22.5 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): N/A

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

All participants will be required to complete a modified version of the UBACC in order to enroll in the study, as described above. 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.

The UBACC may 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 14 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.

22.7 Adults Unable to Consent: N/A

23.0 Setting

23.1 Research Sites:

This research will be conducted online. Participants will self-identify in response to advertisements posted online, using websites such as craigslist, Reddit, NAMI, and similar web pages. Research staff will primarily be located at the University of Minnesota but may work remotely. Research interviews will be conducted using Zoom, and data will be entered into REDCap, the Posit Science BrainHQ portal, and

the Test My Brain platform. Staff will utilize University-owned computers to conduct their work.

23.2 International Research: N/A

24.0 Multi-Site Research

N/A

25.0 Coordinating Center Research

N/A

26.0 Resources Available

26.1 Resources Available:

Facilities

Ambulatory Research Center (ARC): The ARC is contiguous with the main department faculty and staff offices and support facilities, as well as the outpatient clinical services of the Department of Psychiatry. Inpatient as well as emergency medical services are located within the same building. The ARC was recently completely renovated. The approximately 3,700 square feet facility includes all essential elements for the conduct of clinical research. The renovations include the latest IT services, equipment and resources. On entry, there is a comfortable waiting and reception area. There are 5 subject interview rooms that are available for scheduling of candidate/subject study visits. There are two specialized human laboratory evaluation rooms adjacent to a monitoring/equipment control room. The facility also includes two rooms for the completion of computerized neuropsychological and other testing. There is a fully equipped medical examination room. Adjacent to the examination room is a fully equipped laboratory for handling blood and urine specimens. This lab includes essential equipment [refrigerator, freezers, centrifuge] and supplies for sample processing. A secondary laboratory for processing and handling has a pass through for obtaining urine samples from an ADA compliant toilet facility. Two large adjoining rooms with badge-keyed access (recording entry and identification) provides secure storage for study files/source documents and additional study supplies. The ARC space includes 24 workstations distributed across several rooms. Adjacent office space is available for additional staff members (use fluctuates with number and size of projects). Additional office space is allocated throughout the Department for projects having intermittent need for ARC resources. The ARC conference room is equipped for telephone and video conferencing equipment. All staff members have essential computers and other resources. The Department of Psychiatry provides all supplemental services and support.

Feasibility of Recruitment: The study team will need to recruit 5-6 participants with recent onset of a psychotic illness per month over a period of 36 months. As approximately 1% of the population has psychosis, there is a large pool of individuals to recruit from nationwide.

Devotion of Time: Several experienced investigators will provide scientific leadership and oversight of this study. Each will dedicate multiple calendar months of effort to the project to ensure that the protocol is executed according to local and federal regulations. Additionally, there will be several full time study coordinators on staff who will be responsible for participant recruitment and retention, conducting assessments, and operating EEG and fMRI equipment.

Training: All research study staff are required to go through extensive in-depth training and supervision prior to conducting any direct interviews or assessments with human subjects for the study. During the first several months of training, research study staff will complete the University of Minnesota Clinical and Translational Science Institute (CTSI) Foundations for Research Professionals, Collaborative Institutional Training Initiative (CITI), Good Clinical Practice (GCP) training, Health Insurance Portability and Accountability Act (HIPAA) training, Data Security, and Crisis Protocol Training. These training sessions will ensure that the research study staff members are fully competent and compliant with the rules, protocols, and regulations associated with conducting human subject research. Research study staff will be trained on the administration and documentation of informed consent/assent and any other assessments involved in the study. Specific protocol training sessions will be given to each research study staff member that is unique to their job title and tasks for the research study at hand. The delegation of authority log and protocol training log will be updated and maintained routinely in the regulatory files. These logs will provide a list of all current and former staff members with their assigned roles for the research study.

Resources for Anticipated/Unanticipated Event: If there are any adverse events that result from study participation, medical care will be made available to all participants. However, bills for services will be charged to the individual or their insurance.

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28.0 Appendix 1: Data Flow Diagram

