R33 MH106748 Physiology-based virtual reality training for social skills in schizophrenia

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(Virtual Reality Training for Social Skills in Schizophrenia - Comparison With Cognitive Training)

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Study Protocol

We were able to show the target engagement in the R21 phase of this study. The major goal of the R33 phase is to prepare for a future randomized controlled clinical trial (RCT) by piloting a feasibility study that includes an active control arm and multimodal pre- and post-treatment measures. We aimed to achieve the following: (1) test the feasibility of recruiting, randomizing and retaining patients for VR social skills training; 2) compare the social skills training VR compared an active control VR game by measuring behavioral and neural changes after VR intervention.

R33 PROJECT DESIGN

This is a small pilot study to compare the outcome measures after the VR social skills training compared with an active control video game. Participants with schizophrenia (SZ) undergo training. Participants with schizophrenia are randomly assigned to the social skills VR condition or the active control condition at baseline. After completing all the baseline assessments including clinical symptoms ratings, social cognitive assessments, and resting state fMRI scan, participants are asked to visit the lab for 8 sessions (twice a week) to complete the VR training or the active control condition. After 8 sessions, there is a post-training assessment that includes symptoms ratings, social cognitive assessments and resting state fMRI scan. Then participants cross over to the other condition for 8 sessions, after which there is a final post-training assessment. Demographically matched control participants are recruited to obtain comparison data but they do not undergo any training. Research staff conducting clinical symptoms and social functions assessments are blind to the VR training or control condition assignment.

VR Condition: The same procedure as outlined in R21 phase with the determined optimal dose of 8 sessions administered over 4-5 weeks.

Active Control Condition: We control for the number of lab visits, duration of game playing and computer use in the active control group by administering a commercially available video games which do not require any simulated social interactions but instead, support cognition.

Participants:

This proposal involves testing individuals with schizophrenia (SZ), and healthy control subjects (CO). All subjects are recruited from Nashville area. The following general inclusion/exclusion criteria apply to all subjects: (1) no diagnosed organic brain disease, brain lesions, history of head traumas, hormonal disorders, neurological disorders or other conditions that involve the degeneration of the central nervous system (e.g. multiple sclerosis), (2) no substance/alcohol abuse/dependence during the past 1 year, (3) no tardive dyskinesia, (4) WASI IQ> 85. Low IQ makes it less likely that the participants understand the instructions and comply and thus, might introduce confounding factors. Since we need to establish the initial feasibility and acceptability, it is essential that they understand the training instructions. Therefore, we only included those participants with IQ > 85 and those who are able to travel to

the lab independently. Any co-existing medical conditions (e.g., diabetes), smoking habits, and medications were noted. Diagnostic interviews (SCID) were conducted for Axis I for all subjects.

Inclusion/exclusion criteria for schizophrenia group: Participants were recruited from outpatient day facilities in Nashville. DSM-5 criteria were used to diagnose SZ. Those with a history of head injury, substance abuse, neurological diseases (e.g., stroke, tumors), hormonal disorders (e.g. Cushing's disease) or IQ<85 will be excluded. All patients were taking antipsychotic medications. When someone is very psychotic, any social remediation training is not going to be effective. Recruiting outpatients who are stabilized on medication, allowed us to work with the population whose psychotic symptoms are partially in remission but are still experiencing significant social cognitive impairments. The range of symptoms scores of our outpatient sample in the past 14 years in Nashville is very comparable to the scores reported by other groups. The mean SAPS score of our SZ outpatients from the past 14 years was 15.34 (S.D.= 8.36) and the mean SANS was 23.71 (S.D.=14.73). These scores are almost identical to the published mean SAPS (16.8, s.d.=14.2) and SANS (23.0, s.d.=14.6) scores from the FBIRN consortium[143]. For this R33 study, if the SAPS or SANS score is 1 s.d. above the mean of our typical outpatient sample (i.e. SAPS > 23; SANS > 38), we planned to place that patient on a wait list until his/her symptom scores fall within 1 s.d. of the mean. This additional precaution should be able to address potential concerns that psychotic individuals may be adversely affected by virtual reality video games. (See below). One note of concern is the potential adverse effects of the COVID pandemic. This study was on hold for 2 years during the pandemic because we were unable to open the lab to test and train participants due to the concerns of infection. After the study was able to start in 2021, we noted worsening of physical health of the SZ individuals who had consented to participate prior to the pandemic.

Inclusion/exclusion criteria for the healthy control group: Healthy participants were recruited from the Vanderbilt University web-based recruitment panel and from Nashville Metro area via signs placed in public buildings (e.g. supermarkets, Laundromats, gyms, cafes). Exclusion criteria were: Axis I psychotic disorders in themselves or their families (e.g. schizophrenia, bipolar disorder), history of head injury, substance abuse, neurological diseases (e.g., stroke, tumors), hormonal disorders (e.g. Cushing's disease) and IQ<85.

Additional screening for neuroimaging in R33: There are further exclusion criteria for fMRI in the R33 phase because those at primary risk from exposure to high-intensity magnetic fields must be excluded. Exclusion criteria are implanted medical devices (e.g. pacemakers, cochlear implants, IUDs), implanted paramagnetic prostheses, and augmentations (e.g. steel pin). People at secondary risk are also excluded (e.g. asthma, heart disease, diabetes etc). Potential participants must fill out the standard questionnaire used with all patients undergoing MRI at the Vanderbilt University Medical Center. If a potential participant meets the criteria for inclusion in the fMRI component, he/she will go through the informed consent procedure for neuroimaging. If a participant does not meet the inclusion criteria for fMRI part, he/she will not participate in the neuroimaging but will participate in all other parts provided that he/she meets the inclusion/exclusion criteria described above.

Age range: Included age range was 18 and 65. In our actual recruited sample the youngest participant was 20. Aging increases the likelihood of introducing confounding factors such as cognitive decline, dementia, hormonal changes and others. This age group will be

familiar with video games and computers. This is important because the VR training and active control training are similar to video games.

Ethnic composition and diversity: Nashville metropolitan area is increasingly ethnically diverse. We tried to recruit ethnically representative samples of SZ and CO. In our past studies in Nashville, about 20% of our participants were African-Americans.

Gender: We aimed to recruit 50% women.

Procedure: All participants undergo baseline assessments at T1, including fMRI. The research staff conducting assessments are blind to the treatment groups and those who supervise the training session do not do assessments. SZ play the VR game or active control game in the lab. The VR dosing was determined in the R21 phase (8 sessions). After the completion of the training, they are given the post-training assessments and then switch over to the other condition for 8 sessions. We use the same dose for the active control condition. The VR and control game performance scores are saved at each session. To boost adherence, we text 1 day before and 2 hours before the visit. Subjects are paid per session and receive a small bonus at the end of the training. An exit interview is conducted to find out about acceptability and engagement.

Measures: At baseline (T1), we assess social cognitive functions, symptoms and conduct a resting state fMRI scan. To elucidate the mechanism of change, we focus on the social attention and the integrity of the social brain network that supports social cognition. Training begins within a week of completing the assessments. Within a week of the completion of the training, we conduct post-treatment assessments. Next, SZ participants cross over to the other condition and complete 8 sessions, after which they undergo another post-training assessments. Control participants complete only the baseline assessments.

Data Analysis Behavioral Measures: The same general framework as those described for the R21 phase were used. We use univariate and multivariate mixed effects models (LMMs) to assess the effects of the VR intervention relative to the control game condition on the social assessment and symptom measures and other measures noted above (see below for fMRI). We assess effects both at post-Intervention for the VR condition and compare them with the post-intervention after the active control condition. As described in the R21 phase, we will also conduct intensive analyses within the VR condition of the trajectory of performance across 8 sessions of the social skills training. Using structural equation modelling approaches that are appropriate for the moderate sample size, we will further conduct mediational analyses assessing the important question of whether changes in social attention and in the trajectory of performance during training mediate the effects of treatment on social functioning and symptoms. As in the R21 phase, we will also compare post-treatment SZ to normative distributions, and model drop-out and attrition.

Neuroimaging data: VR task provides extensive opportunities to exercise social attention and simulation. We will examine the activity of the pSTS, IPL, and IFG in relation to social attention and social functioning. Our past work indicates that action imitation and simulation deficits in SZ[38,39,117] but repeated practice improve performance[39]. Furthermore, a recent study showed

that simulation work exercises in VR significantly improved work function in real life. We will examine resting state functional connectivity data in relation to the primary outcome measures. ***Data Acquisition***: A Philips Intera Achieva 3T scanner is used to collect high-resolution T1 anatomical images (170 slices; 1x1x1 mm), and T2*-weighted functional images parallel to the AC-PC line (gradient-echo T2*-weighted EPI; 25 slices; TR=2000ms;TE=35ms,flip angle=79˚; FOV=240x240mm^2; voxel size =1.875x1.875x5mm^3). ***FMRI data analysis*:** BrainVoyager QX1.1 is used. Anatomical volumes are transformed into a common stereotactic space[91], and functional volumes for each subject are aligned to the transformed anatomical volumes. Standard pre-processing is performed: temporal high-pass temporal frequency filtering, linear de-trending, 3D motion correction, slice scan time correction, and spatial smoothing with a 6mm Gaussian kernel (full width half-maximum). Individual subject analyses are performed using a GLM with the 6 experimental conditions entered as regressors, and data are collapsed across runs. First, we compare SZ vs. CO at baseline to determine the integrity of the social brain network (group-by-instruction-by-stimulus type mixed-effects analysis) at resting state. Statistical maps are created for each group separately and for the group comparison. Multiple comparisons are corrected at p=.05 by Monte Carlo simulations to arrive at a cluster threshold. We will compare the pre- and post-treatment cortical activity patterns for each treatment regimen. We will also assess the relation between changes in activation of the social brain network and in social attention on the behavioral task and whether such changes predict changes on social outcome measures.