CDA
Motivational Negative Symptoms in Schizophrenia: Intervention and Biomarkers

Specific Aims
Despite substantial advances in pharmacological treatments for schizophrenia (SCZ), it remains the 6th leading cause of disability in the world. More than 102,000 Veterans receive treatment for SCZ through the VA, comprising one of the largest groups of disabled Veterans and accounting for 16-20% of the VA’s health care budget. Quality of life for Veterans with SCZ is significantly impacted as evidenced by few and poor social relationships, negligible community integration, and employment rates fewer than 20%. The negative symptoms of SCZ (i.e. avolition, anhedonia, asociality) are primary determinants of these functional impairments but there are currently no objective assessment tools or validated treatments uniquely designed to target negative symptoms. Developing such treatments and identifying neurophysiological biomarkers to measure negative symptoms are critical public health goals. In line with the recent shift to recovery-oriented approaches for serious mental illness, addressing this unmet treatment need should result in improved community functioning.

Negative symptoms include affective expression-related deficits as well as motivation-related deficits. It is the motivational negative symptoms to which functional deficits are attributed. According to the widely accepted cognitive-behavioral model of negative symptoms, on which the current proposal is based, defeatist beliefs (e.g., overgeneralizations about one’s inability to perform tasks) directly contribute to poor motivation in SCZ. The primary goals of this proposal are to adapt and implement an evidence-based intervention for motivational negative symptoms, and to evaluate potential neurophysiological biomarkers to use as measures of motivational negative symptom severity and treatment response. Motivational Interviewing (MI) is an effective treatment approach for increasing motivation and commitment to new behaviors in a range of areas including substance abuse, treatment adherence, exercise, and gambling. It has also been adapted and shown to be feasible for Veterans with psychotic disorders. This CDA is designed to combine MI techniques with group-based cognitive-behavioral therapy techniques in a randomized controlled trial (RCT), and to examine neurophysiological measures as potential biomarkers of motivational negative symptoms.

More specifically, the scientific goals of this proposal are to: 1) manualize and evaluate the efficacy of a group-based MI intervention on motivational negative symptoms for Veterans with SCZ, and 2) to examine potential neurophysiological biomarkers (i.e., pupillometry and electroencephalography (EEG)) of motivational negative symptoms. The exploratory goal is to test a causal pathway between defeatist beliefs and motivational negative symptoms. To address these questions, 100 Veterans with SCZ who have high levels of motivational negative symptoms will be randomly assigned in a 1:1 ratio to MI or a standard treatment (relaxation skills training; RST). Both treatments will consist of weekly 60-min group sessions for twelve weeks. The assessments will be administered at baseline, at completion of treatment, and at 3-month follow-up.

Specific Aim #1: To adapt the existing MI approach for a group-based treatment for motivational negative symptoms in Veterans with SCZ and to assess its feasibility (i.e., tolerability, participation, satisfaction).
Specific Aim #2: To examine the treatment effects of MI compared to the control procedure on motivational negative symptoms and functional outcomes.
Hypothesis 2a: Individuals who receive MI will have significant improvements in motivational negative symptoms, compared to those who receive the control.
Hypothesis 2b: Individuals who receive MI will have significant improvements in aspects of functioning including social, instrumental, and independent living domains, compared to those who receive the control.

**Specific Aim #3**: To examine neurophysiological biomarkers (i.e., EEG and pupillometry) of motivational negative symptom severity and treatment response.

Hypothesis 3a: At baseline, subjects with more motivational negative symptoms will have more attenuated EEG and pupillary measures.

Hypothesis 3b: Change in the biomarkers over study duration will correlate with change in clinical ratings of motivational negative symptoms.

**Exploratory Aim**: To explore a causal model by examining whether MI improves defeatist beliefs compared to a control procedure.

Although MI is a well-established intervention for a range of clinical populations and conditions, the proposed project will be the first examination of MI in a group format for negative symptoms in SCZ. If the proposed study finds a significant treatment effect, next steps would include applying for funding to conduct a larger trial, develop a training manual for dissemination, and testing the treatment in other VA populations with motivational and functional deficits (e.g., traumatic brain injury, post-traumatic stress disorder). The project has high potential to benefit Veterans with disabling mental illness and would also facilitate my independence as a VA researcher and professional resource equipped with a unique combination of skills.

### 2. Research Plan

#### 2.3 Research design and methods

##### 2.3.1 Subjects

One-hundred participants with SCZ and schizoaffective disorder will be included in the study. Our sample will consist of Veterans who will be recruited from VA outpatient treatment clinics through staff presentations and referral. All recruiting efforts will be coordinated through Dr. Green’s laboratory. The availability of recruitment infrastructure, trained clinical interviewers, and neurophysiological assessment equipment will greatly facilitate the conduct of the project. The laboratory has had a successful history of meeting recruitment goals outlined in funded VA and NIMH projects. Approximately 8-10 patients with a SCZ/schizoaffective diagnosis are admitted to GLA clinics each week. Potential participants will be told that the purpose of the study is to develop a treatment to make daily life better by working on goals or dealing with stress. Veterans who are interested in the study will be screened for general inclusion and exclusion criteria by the recruiter using HIPAA compliant procedures.

We will select clinically stable Veterans with SCZ and high negative symptoms between the ages of 20 and 55 years old. Participants will be considered clinically stable if they had no medication changes in the past six weeks, no psychiatric hospitalization in the past three months, and no changes in housing in the past two months. We will use a negative symptom scale (i.e., Clinical Assessment Interview for Negative Symptoms [CAINS; 7]) with a well-validated motivational negative symptom subscale to determine eligibility based on negative symptoms. To guide the quantitative cutoff for inclusion we examined data from the CAINS that was administered to 162 patients in our lab in a previous study. The mean for the Motivation and Pleasure (MAP) subscale was 16 and the median was 15, thus 15.5 will be the negative symptom cut-off score for the proposed study. We recently used this approach successfully for recruitment into the effort-based decision-making study described above (Section 2.2.2).
Exclusion criteria will include having an estimated premorbid IQ below 70 based on reading ability, having an identifiable neurological disorder, seizures, or history of serious head injury, meeting criteria for substance dependence in the past 6 months or abuse in the past month, being insufficiently fluent in English as determined by the participant’s ability to understand the consent form, or having low levels of motivational negative symptoms. Most of the participants will be chronic and medicated, though we will not select patients based on chronicity. Duration of illness and medication information will be obtained through self-report and examination of medical records. All psychoactive medications and their dosages will be carefully recorded. Antipsychotic medication dosages will be converted to chlorpromazine (CPZ) equivalent units, which can be used as covariates in statistical analyses.

2.3.2 Randomization and treatment procedure
Participants will be randomly assigned to either the group-based MI treatment or the control treatment (designed to control for the effects of attending a group, contact with research personnel and peers, and financial compensation for participation). To optimize power for the comparison between the treatments, we will use a 1:1 randomization procedure resulting in a total of 50 subjects in the MI group, and 50 in the control group. Subjects will be randomly assigned in blocks of 10 (5 in each condition) to maintain balance throughout the study. The MIRECC Data Core will create an online randomization system for the project, which will be accessible only to the study coordinator who will perform the assignments. The testers will be blind to treatment condition. Randomization will be programmed in ASP (Active Server Pages).

The study will consist of 12 weeks of active intervention with once-weekly 60-min group sessions. After participants are assigned to a condition, the study coordinator will schedule the days and times of the groups, according to participants’ availability. To ensure optimal attendance, reminder calls will be made the day before group sessions and transportation vouchers will be available. Following treatment, subjects will be scheduled for a post-treatment visit within 2 weeks of the last group session. This visit will last approximately 2.5 hours and will include the same clinician-rated, performance-based, and neurophysiological assessments of motivational negative symptoms, as well as cognitive, functional capacity, and community functioning measures. Three months after the post-treatment visit, participants will return for a final comprehensive assessment of negative symptoms, cognition, and community functioning. Overall, the study will consist of screening plus 3 assessment visits (11 hours total) and 12 group treatment sessions (12 hours total). Subjects will be compensated $15/hour for the interview and testing sessions (first 2 visits and post-training visits) and $10/hour for the treatment sessions, a rate deemed acceptable by our IRB. Although it is possible that paying for group attendance reduces external validity, the payment rate is roughly equivalent to minimum wage in California. Within the context of this initial efficacy and feasibility trial it is appropriate to compensate participants for their time, since we cannot guarantee any treatment benefit.

<table>
<thead>
<tr>
<th>Table 1: Enrollment for Each Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Screening, MI, assessments</td>
</tr>
<tr>
<td>Screening, control group,</td>
</tr>
<tr>
<td>assessments</td>
</tr>
</tbody>
</table>

Recruitment will be ongoing and we expect to enroll 20 subjects/year for 5 years (see Table 1). Based on dropout rates in our previous training intervention studies, we project 20% attrition, which will leave us with an estimate of at least 80 completers: 40 getting the MI intervention, and 40 getting the control intervention. We will make every effort to maintain Veterans in the
study protocol while emphasizing that their participation is strictly voluntary and that they can withdraw at any time. To minimize attrition, we will inform subjects that they will be in the groups for 3 months but will be enrolled in the study for 6 months, to ensure that they will not be leaving town or relocating during the study period. We will contact those who opt to discontinue treatment to request that they participate in a final outcome assessment. Details of the plan for handling missing data and minimizing potential threats to randomization caused by differential dropout rates are further described in the data analysis section.

Administrative Database Recruitment

In addition to recruiting in clinics and board and cares, we will also access the VA VINCI administrative database to help identify Veterans with schizophrenia/schizoaffective disorder who are currently receiving care at GLA. We will request the following kinds of data from the VINCI database: real SSNs, mental health stop codes containing relevant ICD 9 and 10 diagnosis codes for Veterans with diagnoses of schizophrenia/schizoaffective disorder as well as attending a GLA appointment within the past 12 months.

Once identified by the database data pull, Veterans will be invited by a recruitment letter sent by mail to participate in the study. If they choose to contact research staff, or opt to participate in the study after receiving the recruitment letter and a phone call from research staff, Veterans will be given an appointment for an interview. Informed consent and HIPAA authorization will be obtained by research staff before any study procedures are begun.

Once identified by the database data pull, Veterans will be invited by a recruitment letter sent by mail to participate in the study. If they choose to contact research staff, or opt to participate in the study after receiving the recruitment letter and a phone call from research staff, Veterans will be given an appointment for an interview. Informed consent and HIPAA authorization will be obtained by research staff before any study procedures are begun.

Veterans will receive the letter and the flyer for the study in the mail. In the letter it will state that the Veteran can contact the recruitment office if they are interested in participating in the study. They will also be informed they can call the recruitment office to opt out of participating in the study and to request no further contact by study staff. The letter will inform the Veteran that if the recruiters don’t hear from them they will give them a call in 2 weeks to follow up. Our staff will not contact any Veteran more than 3 times total (1 letter and 2 phone calls).

Data downloads for recruitment purposes from the VINCI database will be stored on a secure VAMC MIRECC server and accessed using VA password-protected computers. Paper files will be stored in locked file cabinets in the offices of the West Los Angeles VA MIRECC, in Building 210.

We have completed waivers of authorization and consent for this recruitment screening, but none of this information will be included in study data, and no PHI will be gathered from subjects until they have signed consent and HIPAA authorization.

2.3.5 Assessments

During the first visit (approximately 1.5 hours), participants will be screened and receive a standardized diagnostic interview to ensure eligibility. Participants who fit selection criteria for the study will be scheduled for another visit. During the second visit, (approximately 4.5 hours), subjects will be consented and administered a battery of clinician-rated, performance-based,
and neurophysiological assessments of motivational negative symptoms, as well as cognitive, functional capacity, and community functioning measures (see Table 2).

The MCCB cognitive assessment is repeated in another study: Homeless Veterans with Mental Illness: Predicting and Enhancing Recovery, (Green, 0023). In order to reduce subject burden and preserve the validity of these assessments, a participant who enrolls in both of these studies within a 3 month period will share his assessment data for this task from the first study he enrolls in with the other study in which he later enrolls. None of the source document shared data will leave the VA space where it will be collected and stored. The research lab infrastructure for Drs. Green and Reddy are shared: research lab space, methods, and assessment and data entry/storage computers are identical for both studies, and the personnel overlap to a very large extent.

Table 2. Summary of Assessments

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Time Estimate</th>
<th>Screening</th>
<th>Baseline</th>
<th>Post-treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnostic/Demographic/Cognitive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structured Clinical Interview- DSM-5</td>
<td>75 min</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric &amp; Social History Form</td>
<td>15 min</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MATRICS Cognitive Battery (MCCB)</td>
<td>75 min</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UCSD Performance-based Skills Assessment (UPSA)</td>
<td>25 min</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Brief Psychiatric Rating Scale (BPRS)</td>
<td>15 min</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Negative Symptoms and Defeatist Beliefs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Assessment Interview for Negative Symptoms (CAINS)</td>
<td>30 min</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dysfunctional Attitudes Scale</td>
<td>15 min</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Functional Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific Level of Function (SLOF)</td>
<td>30 min</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Neurophysiological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive effort pupillometry</td>
<td>20 min</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>EEG reward (FN) &amp; flanker (ERN) tasks</td>
<td>20 min</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Total time:</strong></td>
<td>1.5 hrs</td>
<td>4.5 hrs</td>
<td>2.5 hrs</td>
<td>2.5 hrs</td>
<td></td>
</tr>
</tbody>
</table>

2.4 Statistics and power analysis

2.4.1 Data management

Data management and statistical support will be provided by the VISN 22 MIRECC Data Core, directed by our statistical consultant, Dr. Sugar. The data core is made up of multiple senior consulting faculty from the UCLA Departments of Biostatistics and Psychiatry as well as full-time staff statisticians, database and applications programmers, data managers and web designers. Its personnel have extensive experience supporting studies ranging from small pilot projects to large multisite centers and have a long history of collaboration on SCZ studies at GLA with Dr. Green’s lab. For this project, the data core will develop a customized VA intranet-based data system, including the subject registry, data dictionary, randomization system, data entry forms, project management tools and the centralized database which can accommodate both manual entry and electronic upload and merging of data from other sources. In particular, EEG and pupillometry data will be collected and processed on a separate computer, and the primary ERP amplitude and pupil dilation measures will be extracted and uploaded into the primary database. The system will be housed on the data core’s secure VA servers and will
feature numerous security and quality assurance features including double entry to verify data correctness, automatic logic and range checking, and strict protocols for data confidentiality, transfer and back-up including anonymized ID coding to protect subject privacy. All files are encrypted and the systems and tools are protected by 128-bit SSL, the secure socket layer technology used for sensitive transactions on the web. The system will be accessible only via the VA intranet and will employ a hierarchical system of password-protected logins, allowing differential access to project team members as appropriate to their roles. Data will be accessed only through the system, not transported, and analyses will be performed on de-identified and aggregated data in consultation with the MIRECC Data Core.

2.4.2 Statistical plan and missing data

The experimental design for this study is a 2-group RCT, with assessments at baseline, post-treatment, and 3-month follow-up. The aims correspond to a comparison of the effects of the active treatment to a control condition on motivational negative symptoms as well as community functioning, and to examining pupillometric and ERP variables in relation to negative symptom severity and treatment response. For each of these outcomes, we specify a primary measure. For negative symptoms we will use the total score from the Motivational and Pleasure subscale of the CAINS, for functional outcome we will compute three composite scores for the three domains of functioning assessed with the SLOF. The pupillometry measure will be a difference score in pupil diameter for the hard versus easy trials. The main EEG measures will consist of the ERN amplitude at electrode FCz/Cz from response onset to 100 ms (i.e., 0-100 ms), and FN amplitude at electrode FCz/Cz from 250-350 ms from the onset of the feedback stimulus. To further characterize the treatment response profiles, exploratory analyses will be performed to examine the effects of the intervention on dysfunctional beliefs measured with the DAS. We are well aware of the risk of Type I error inherent in a study with a battery of assessments and have protected against it by clearly specifying a limited a priori set of primary outcome measures and contrasts of interest and designating all others as exploratory. However, since this is a preliminary study, designed to obtain estimates of treatment effects and to identify optimal intervention components and measures for a future definitive efficacy study, it is equally important not to miss any potentially relevant outcomes. All results will therefore be reported using an uncorrected two-sided significance level of α=.05.

Prior to performing the primary analyses, descriptive statistics and graphical summaries will be obtained for all outcomes to check for missing data, outliers and the need for transformations or nonparametric methods. To assess the success of randomization, t-tests and chi-square tests will be used to test for baseline group differences on the primary outcomes as well as on demographic (age, gender, parental/personal education) and clinical (medication, duration of illness, and symptom severity) characteristics and neurocognitive functioning. Measures that show significant differences will be included as covariates in subsequent analyses. Below we give a detailed description of the analytic plan by specific aim.

We plan an intent-to-treat approach, using all available data from all subjects, regardless of the degree of treatment participation. For the multilevel modeling (MLM) analyses, the PROC MIXED modeling approach uses the missing at random (MAR) assumption. This is optimal because in the case of attrition and missing data, data will be included for each person who has complete data per each occasion, and thus people are not disqualified from the analyses if they missed one occasion. The goal is to make valid inferences about the population parameters despite bias introduced by attrition; the goal is not to recover the missing data values. The models, therefore, represent the means and change rates according to the data that are present. Missing data points are not imputed.

In this study population there is likely to be moderate data loss (up to 20% due to attrition and EEG artifacts based on our prior experience) and we recognize the potential for bias due to differential dropout. We will use chi-square tests to determine whether dropout
status is predicted by baseline variables or treatment condition. If there is evidence that attrition
patterns might introduce bias into the analyses, we will perform supplementary analyses adding
propensity-score adjustments to the primary models. In the propensity score framework,
baseline characteristics are used to develop a predictive model for attrition (e.g., via logistic
regression), and the probability of dropout is used either as a covariate or to weight the
observations in the subsequent models. In essence, cases that are similar to dropouts are
weighted more heavily to "make up" for others like them who dropped out. We will also explore
treatment dosage (attendance) as a covariate in secondary models.

General analytic approach
To make the most efficient use of our data, the primary analytical technique will be MLM.
Advances in longitudinal research suggest that MLM models should be used for data where
observations are not independent to avoid violating the assumption that the standard errors for
each time point are not correlated. The recommended approach is to model individual change
across time and then examine the effects of covariates to see if there are systematic differences
in rate of change [85]. MLM involves modeling at two levels: the lowest being the within subject
(e.g., Veterans negative symptom scores on multiple occasions), which is grouped by the
between subject (e.g., group). At Level 1 each individual’s scores on the outcome measures are
regressed on time or a transformation of time. At Level 2, the Level 1 parameter estimates of
the slope are treated as criterion scores and each is regressed on the covariates. Final
estimates of the growth curve parameters for each individual are derived; this yields growth
curve parameters for each individual that are a combination of the within subject (Level 1) and
between subject (Level 2) estimates [86].

MLM accounts for correlations induced by repeated measures within subjects, it allows
for both fixed and time-varying covariates, and it automatically handles missing data producing
unbiased parameter estimates provided that observations are missing at random. This allows us
to include all available data from all subjects in the analyses, regardless of the degree of study
participation or treatment dosage received, consistent with the intent to treat framework. For
each of our primary outcomes (motivational negative symptoms and functional outcome
domains) our core model will include time (baseline, post-treatment, 3-month follow-up) nested
within the individual and the individual nested within group (MI or RST) as the within subject
factor, and a group by time interaction. Our primary hypotheses correspond to the group by time
interactions comparing the outcome trajectories, or rates of change, for MI and RST.

Analysis plan by specific aim
Specific Aim #1: To adapt the existing MI approach for a group-based treatment for
motivational negative symptoms in Veterans with SCZ and to assess its feasibility (i.e.,
tolerability, participation, satisfaction).

Specific Aim #2: To examine the treatment effects of MI compared to the control procedure on
motivational negative symptoms and functional outcomes.
  Hypothesis 2a: Individuals who receive MI will have significantly larger improvements in
  motivational negative symptoms, compared to those who receive the control.
  Hypothesis 2b: Individuals who receive MI will have significantly larger improvements in
  aspects of functioning including social, instrumental, and independent living domains,
  compared to those who receive the control.

Specific Aim #3: To examine neurophysiological biomarkers (i.e., EEG and pupillometry) of
motivational negative symptom severity and treatment response.
  Hypothesis 3a: At baseline, subjects with more motivational negative symptoms will have
  more attenuated EEG and pupillary measures.
  Hypothesis 3b: Change in the biomarkers over study duration will correlate with change in
  clinical ratings of motivational negative symptoms.
**Exploratory Aim:** To explore a causal model by examining whether MI improves defeatist beliefs compared to a control procedure.

2a: For this aim we will use MLM across the three time points with motivational negative symptoms as the within subject dependent measure and group as the between subject independent variable. Our hypothesis is the MI group will show a decrease in negative symptoms over time, on the individual level and compared to the RST group.

2b: For this aim we will use MLM across the three time points with the functional outcome domain scores as the within subject dependent measure and group as the between subject independent variable. Our hypothesis is the MI group will show significant improvements over time, on the individual level and compared to the RST group.

3a: For this aim we are going to use MLM as in the aims above, but include biomarker levels at baseline (EEG peak amplitudes and pupil diameter difference score) as covariates on the within subject level. Our hypothesis is that the biomarkers are associated significantly with negative symptom change over time.

3b: For this aim we are going to use MLM as in the other aims above, but include biomarker levels (ERN peak amplitude and pupil diameter change) as covariates on the between subject level, (i.e. we allow different levels of this covariate for each time point for each individual). Our hypothesis is that the biomarkers are associated significantly with the symptom severity at each time point, suggesting that they change in parallel.

**Exploratory aim:** For the exploratory aim, we will use MLM across the three time points with the defeatist beliefs subscale score as the within subject dependent variable and group as the between subject independent variable. If there is significant change in defeatist beliefs we will include the defeatist beliefs score in a causal path analysis model between group and outcomes.

**2.4.3 Power considerations**

We plan to enroll 100 subjects (n=50 for the treatment and control conditions) to obtain a final sample of n=80 subjects with complete data after accounting for attrition and data loss. Power calculations are conservatively based on these numbers and assume a two-sided significance level of $\alpha=.05$. We also assume a within-subject autocorrelation of $r = .7$, a value based on our experience with similar studies in the past. Our primary hypotheses all involve comparisons of the change over time between the two treatment groups. Our design provides over 80% power to detect overall effects as small as $\text{f}^2=0.01$ (a small effect size) which is roughly equivalent to a pattern of change in the two study arms for which the difference between groups is 0 at baseline, and $d=.5$ at study endpoint, with the measurement at time 2 between these two values. In addition, we note that we have over 80% power to detect within group changes from baseline to end of treatment of $d = .4$ in the treatment group, which is considered a medium effect size using the conventions of Cohen. Since we are powered to detect small to medium effect-sizes, we should be in a strong position even if effects are smaller on the symptom and functioning measures. Thus, the proposed sample size should provide adequate power to evaluate the primary hypotheses, and to detect effect sizes similar to those in previous negative symptom intervention studies. In addition, the proposed sample size is larger than the majority of existing studies in this area.