Physical Exercise Effects on Determinants of Social Integration in Schizophrenia

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NCT02716584

August 12, 2019

A. Background and Significance

Impairments in social integration are considered a hallmark of schizophrenia and constitute a huge mental health problem. Studies show reduced marriage rates, few friendships, and a higher frequency of living alone resulting in chronic social isolation [1-3]. Poor social integration reduces Veterans' engagement with case management, medical and mental health care, increases risk for suicide, and leads to early mortality. A meta-analysis examined prospective all-cause mortality data across 148 studies (over 300,000 participants) with an average follow up of 7.5 years. Results for social integration revealed that the odds ratio for survival was .64, meaning a 36% reduction in the odds of survival for those with inadequate social integration [4]. The effect size is comparable to that of smoking, and greater than obesity and alcohol abuse. To gain traction on this problem, treatments will be needed that target determinants of poor social integration.

A.1 Determinants of Social Integration in Schizophrenia: Cognition and Affect

Two leading determinants of poor social integration in schizophrenia are impairments in cognition and disturbances in affect. Cognitive impairments are a core feature of schizophrenia [5, 6]. They are generally stable across the adult lifespan until age 65 when there is evidence for accelerated decline [7]. Impairments are found in attention, working memory, verbal and visual learning, reasoning and problem-solving ability, speed of processing, and social cognition [8]. Meta-analyses reveal medium to large effect size relationships between selected areas of cognition and community functioning in schizophrenia [9-11]. Importantly, cognition is related to a number of abilities involved in the processing of social information such as understanding the thoughts, intentions, and actions of others, verbal communication, and social problem-solving skills [12].

Schizophrenia is also characterized by disturbances in trait affectivity (i.e., basic emotional dispositions). Adult personality traits can be divided into 2 dimensions: positive and negative affectivity [13]. People high on positive affectivity experience more positive emotions (e.g., happiness, joy), and approach life more actively, with energy and enthusiasm. They seek out and enjoy the company of others. In contrast, people with high negative affectivity experience negative emotions (e.g., sadness, despondence), and view the world as problematic, threatening, and distressing. They tend to be more reserved and socially aloof. As a group, individuals with schizophrenia tend to show stably low positive affectivity and elevated negative affectivity throughout the course of illness. These traits are linked to a range of real-world behaviors including poor social engagement and activity, and account for significant deficits in social adjustment independent of cognition [14].

### A.2 Benefits of Physical Exercise on Cognition and Affect

Reviews and meta-analyses support the benefits of physical exercise (PE) on both cognition and affect. Benefits are observed in studies of normal aging, mild cognitive impairment, neurodegenerative diseases, oncology, depression, and bipolar disorder [15-18]. For cognition, PE is associated with improvements in attention, working memory, verbal learning, speed of processing, and executive control [15, 19] with some data showing corresponding brain-related changes in hippocampal volume and brain-derived neurotrophic factor (BDNF) signaling [20-22]. PE is also associated with higher levels of positive affect in patients with depression and dementia, as well as in healthy sedentary adults [23].

The majority of studies of PE in schizophrenia have focused on changes in physical health and psychiatric symptoms [24, 25]. The schizophrenia literature for PE effects on cognition and affect is small, but developing. A recent PubMed search (July, 2015) revealed 3 RCTs on the effects of PE on cognition [26-28], one on affect [29], and none on both cognition and affect together. All studies were non-VA samples with mean age of participants 40 years or less, and examination of response predictors was limited to one variable.

For this SPiRE proposal, we intend to address this gap in scientific knowledge by examining the effects of PE on both cognition and affect in a VA sample aged 45-65, prototypical of the aging VA clinical population. In addition, we plan to explore putative predictors of treatment response. If the hypotheses are supported, we will know the value of PE for cognition and affect in middle-aged Veterans with schizophrenia. We view this application as a necessary first step in addressing a broader clinically important question: Ultimately, we wish to see if PE leads to improvements in social integration, but first we need to show that we can gain traction on treating mediators along the pathway to social integration. Should the findings support our hypotheses, data from this SPiRE will be used to support a VA Merit proposal to investigate this eventual goal (see conceptual model in Figure 1).

Figure 1: Conceptual Model for the Effects of Physical Exercise on Social Integration

B. Preliminary Studies

Findings from studies on assessment and rehabilitation treatment relevant to the proposal are presented; feasibility data are presented at the end.
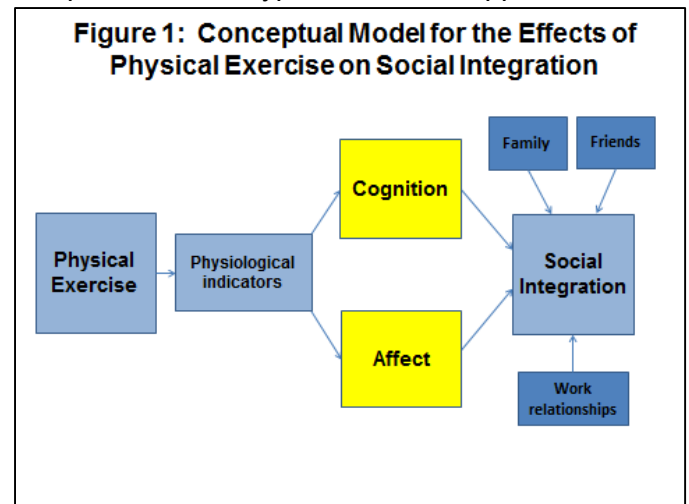
B.1. Assessment of Cognition and Affect

B.1.1 Cognition

Our research lab is recognized for efforts aimed at understanding the relationship between cognitive impairment and community integration in schizophrenia. Findings from one of the PI's early studies revealed ties between selected areas of cognition and rehabilitation outcome [30]. Subsequently, the PI has been involved in schizophrenia studies examining preserved vs. impaired areas of memory functioning [31], cognitive impairment profiles [32], social cognition impairments[33], and the relationship between social cognition impairments and work outcome[34]. Dr. Green, co-investigator on this proposal, has written 3 reviews of the literature examining the relationship between cognition and functional outcome [9, 35, 36]; the PI was co-author on 2 of them. These reviews have had strong impact with 2 of them each receiving over 2,000 citations.

B.1.2 Affect

Our lab has also been involved in research assessing trait affectivity in schizophrenia. Data from a review of trait affectivity measures (Horan and Green) showed that individuals with schizophrenia tend to have stably low positive affectivity and elevated negative affectivity throughout the illness course [37]. Dr. Horan has also examined trait affectivity in 2 other studies: one that examined emotional range associated with the deficit syndrome of schizophrenia, and one that examined trait affectivity in response to psychosocial stress [38, 39].

B.2 Rehabilitation Treatment

B.2.1 Cognitive rehabilitation and work outcome

The PI has been active in psychiatric rehabilitation research for over 25 years. A primary aim has been to improve community integration among individuals with schizophrenia by addressing cognitive impairments that serve as rate-limiting factors to rehabilitation success. Errorless learning, a cognitive rehabilitation intervention that teaches new skills and abilities by compensating for cognitive impairments, was examined in a series of studies aimed at improving work outcome. Results supported the efficacy of errorless learning at improving entry-level job task performance in a simulated work setting [40]. These findings were extended to a more naturalistic setting offering part-time, time-limited transitional work experience [41]. More recent efforts examined the efficacy of errorless learning at improving work performance within VA and community-based supported employment programs. Results from these studies revealed a separate problem: Social difficulties were a greater barrier to employment success than job performance difficulties. Interpersonal problems with supervisors and co-workers were the leading source of problems for Veterans with schizophrenia at their competitive jobs, and were the leading reason for early job termination. These findings provided an impetus for the current proposal. By realizing that training on work performance only solved part of the problem, we wanted to focus on other aspects, such as social integration, that appear to be rate-limiting for vocational success. Further, these findings underscore the fact that poor social integration not only poses a problem in forming close friendships and maintaining family contacts, it also affects functioning in the workplace as well.

The rationale for selecting PE as a treatment intervention stems from our interest in investigating the health benefits associated with work and physical activity. A common element across most Veterans' jobs attained through supported employment is that they involve physical activity, e.g., grounds work, housekeeping. One hypothesis we have entertained is that Veterans who maintain steady employment should be more physically active compared to unemployed Veterans and level of physical activity should be associated with mental and physical health benefits. The current proposal builds on this conceptual idea and targets physical activity directly with an active intervention aimed at improving cardiorespiratory fitness, cognition, and affect as a goal.

B.2.2 Physical activity and health outcome

Dr. Young, co-investigator on this proposal, is currently examining the effects of physical activity on health outcomes. He received a VA HSR&D grant to examine the effects of in-person vs. web-based delivered instructional modules on PE and nutrition in Veterans with serious mental illness who are overweight. Participants are assigned to in-person delivery of the instructional modules (n=95), web-based delivery (n=93), or a control group (n=88) and followed for 12 months. Data collection is ongoing, although all 6 month interviews have been completed and the follow-up rate was 84% (232/276). Primary outcomes include measurements of physical activity, dietary habits, weight change, and health-related functioning. Walking is currently the leading choice of physical activity with a preference to exercise with others rather than alone.

B.3 Feasibility Data on the Walking Exercise Program

For this application, we collected feasibility data on 4 Veterans with schizophrenia (aged 36-59; body mass index (BMI) range = 24.3 - 29.6) drawn from the MIRECC registry (see section C.2 on recruitment) who participated in an abbreviated 4-week version of the proposed walking exercise program (1/3 the length). The walking exercises were instructor-led (PI + study coordinator), held 3 times per week, and conducted in small group format. For weeks 1-2, Veterans walked 20 min per session; for week 3, they walked 30 min per session; for week 4, 40 min per session. We wanted to address 3 questions: (a) Would Veterans with schizophrenia participate in an exercise program of this type? (b) Could the walking exercises be conducted in small group format? (c) Would the 4-week pre-post training data provide a signal supporting improvement in cardiorespiratory fitness? Participation: Of the 4 participants, 2 attended all 12 sessions, one missed one

session due to illness, and one missed 2 sessions due to illness. All 4 stated that they enjoyed the walking exercise and would participate in such a program again if it were available at the VA. Group format: We found some variability in cardiorespiratory challenge needed to attain the target peak heart rate for one of the Veterans. By including 2 instructors and selecting an area of the VA campus with steeper grades we were able to address this need (i.e., the Veteran requiring greater rigor went with one instructor; the others went with the other instructor).

Table 1. Pre-post Training Cardiorespiratory Fitness Data (estimated $V0_{2\ max}$; mls/kg/min)		
Participant	Baseline	Post-training
Subj 1	11.1	12.3
Subj 2	31.1	37.7
Subj 3	24.9	33.3
Subj 4	12.9	20.0

Implemented in this way, all 4 Veterans were able to reach their target peak heart rate on each walking session. Pre-post training cardiorespiratory fitness data: Baseline levels of cardiorespiratory fitness (estimated $V0_{2\ max}$) were all in the "very poor" to "poor" range compared to men in their age group (range = 11.1 to 31.1 mls/kg/min; see Table 1). Following training, each Veteran showed improvement from baseline with increases in estimated $V0_{2\ max}$ of 10.8%, 21.2%, 33.7%, and 55.0%, respectively; 2 Veterans attained a "fair" classification rating at post-training. In sum, the feasibility data suggest that Veterans with schizophrenia will participate in walking exercises; that a group-based, instructor-led format is feasible; and that cardiorespiratory fitness levels can be improved.

C. Research Design and Methods
C.1. Study Timeline
We propose a 2-year study period. The first 3 months will be devoted to training personnel on the test battery, purchasing supplies, and recruitment. The succeeding 18 months will be devoted to data collection and the final 3 months to analyses and manuscript preparation.
C.2 Research Setting and Recruitment
The study will be conducted at the MIRECC Unit within the VA Greater Los Angeles Healthcare System (GLA). The composition of the GLA Veteran population allows recruitment of both women and minorities for the project. Based on previous GLA studies, approximately 90% of participants will be men with an ethnic breakdown of approximately 40% White, 40% African-American, 15% Hispanic, and less than 5% of Asian and other ethnic groups. Ample office and lab space exists within the MIRECC (including a 1,944 square foot day room) for consenting, interviews, testing activities, conducting stretching exercises, and project personnel.

Participants will be recruited using methods approved by the VA Institutional Review Board (IRB). Our primary recruitment strategy will be to draw potential participants from the IRB-approved MIRECC registry. Veterans in the registry are those who have participated in past MIRECC research projects and consented to be contacted about future ones. The registry currently includes 184 Veterans meeting the study's diagnostic and age criteria. As additional sources, MIRECC projects regularly draw from GLA mental health clinics which include the Schizophrenia Clinic, Mental Health Intensive Case Management, Mental Health Services, Dual Diagnosis Treatment Program, and Psychosocial Rehabilitation and Recovery Center. These clinics provide services to an additional 800+ Veterans meeting the study's diagnostic criteria.
C.3. Study Sample
We plan to enroll 54 Veterans with a psychiatric diagnosis of schizophrenia or schizoaffective disorder. Medication type and dose will be left to the discretion of the treating psychiatrist.
Selection criteria:
(a) DSM-5 diagnosis of schizophrenia or schizoaffective disorder; (b) age 45-65; (c) screened for physical health risks (i.e., no serious heart condition, dizziness or falls, bone or joint problems posing safety concerns, ambulatory limitations; or in those cases where a risk is identified clearance is provided by the Veteran's primary care provider or VA psychiatrist); (d) clinically stable (e.g., no inpatient hospitalizations for 3 months prior to enrollment; no change in type of antipsychotic medication in the past 4 weeks); (e) no evidence of substance or alcohol use disorder (moderate to severe) per DSM-5 criteria in the past 3 months; (f) no clinically significant neurological disease as determined by medical history (e.g., seizure disorder); (g) no history of serious head injury with loss of consciousness >1 hour; (h) no participation in an exercise program in the past 6 months; (i) able to understand spoken and written English sufficiently to comprehend consent procedures.
C.4 Study Design
Veterans who are eligible and provide written informed consent will be enrolled. Three cohorts of 18 Veterans each will be assembled over the course of the study with subjects randomized 2:1 to an experimental group (n=36) vs. a control group (n=18). The experimental group will participate in brisk walking exercises; the control group will participate in non-aerobic (non-yoga) stretching exercises matched to the experimental group on duration, frequency, and number of sessions. Within each cohort of 18, we will form 6 triads matched on baseline levels of cardiorespiratory fitness. Within each triad, 2 Veterans will be randomized to the exercise group and 1 to the comparison group. The purpose of the randomization scheme is to maximize balance and power for detecting a treatment effect and explore putative predictors of treatment response. Predictor

variables will include baseline levels of BMI, smoking behavior, symptoms, and motivation (described in section C.5 below). The 3 cohorts will be assembled and run between months 3-21 of the study period (Figure 2).

C.4.1 Implementation of exercise training

In designing the exercise program, we considered personal preference and physical activity risk factors common to Veterans with schizophrenia. The modal, and most preferred, method of exercise in studies of schizophrenia has been walking, using a regimen of 3 times per week in 40-minute sessions over a 3-month period [24, 25, 42]. Our exercise program will include instructor-led brisk walking exercises conducted outdoors in small groups. This method provides a safe way of engaging in PE, but also helps ensure that target peak heart rates can be attained for each Veteran.

Figure 2. Project Timeline

n = 18 per cohort comprised of 2 walking groups and 1 stretching exercise group of n= 6 each;
A = baseline assessment; B = end-point assessment

Both the experimental and control groups will be run in groups of n=6 subjects each. Veterans in the experimental group will participate in walking exercises 3 times per week over a course of 12 weeks. The walking exercises will be conducted on GLA grounds where there is a course mapped out that provides varying degrees of cardiorespiratory challenge (see Appendix 1). Each session will include a 5-min warm-up and cool-down period and stretching exercises. Walking duration will be gradually increased over the 12-week period. For weeks 1-2, Veterans will walk 20 min per session; for weeks 3-4, 30 min per session; for weeks 5-12, 40 min per session (the desired maximum outcome). Walking exercises will be led by 2 research personnel experienced in PE work-outs. Both will carry cell phones with them to alert the PI and a back-up MIRECC investigator should any Veteran experience physical complaints during a walking session. Each Veteran will wear a heart rate monitor (Fitbit ChargeHR) that provides continuous heart rate measurement. Heart rate will be recorded every 10 min during each walking session with the aim of maintaining a target peak heart rate of 60% to 70% of the maximum for the individual's age (i.e., 220-age). Based on our feasibility data, it is likely that our cohorts will include a subset of individuals who will require adjustments in exercise rigor to meet cardiorespiratory challenge. Should this occur, we will divide the groups accordingly into higher and lower functioning subsets, and manipulate exercise rigor in two ways by: (a) implementing a brisker pace, and/or (b) walking uphill. By monitoring heart rate during the walking exercises, our instructors will be able to gauge the need to walk faster, or take routes that include hillier sections of the GLA grounds to provide adequate challenge. Veterans in the control condition will participate in instructor-led, non-aerobic (non-yoga) stretching exercises which will include a 5-min warm-up and cool-down period of slow walking to prevent muscle strain.

C.4.2 Assessment schedule

All participants will receive a baseline and end-point assessment. The baseline assessment will include measurement of cardiorespiratory fitness, cognition, positive and negative affect, psychiatric symptoms, BMI, current and past smoking behavior, motivation, and social integration. This assessment will also include a SCID update to confirm diagnosis and collection of demographic and psychiatric history data. The end-point assessment will be conducted immediately after 12-week participation in the experimental or control condition and include the same measurements as baseline (excluding the SCID update and psychiatric history; see Table 2). Testers will be blind to group assignment. To assess tolerability, we will collect data on sessions completed and drop-outs respective to each group. Qualitative data on the PE program will be collected to learn about participants' likes, dislikes, and suggestions for improvement. Total assessment times are 4.0 and 3.2 hours for the baseline and end-point assessments, respectively (see section C.5 below).

C.5. Assessments

C.5.1 Psychiatric diagnosis. Psychiatric diagnosis will be based on SCID[43] updates of Veterans with schizophrenia or schizoaffective disorder from our MIRECC registry. The updates take about 30 minutes.

C.5.2 Psychiatric and social history schedule. Used across MIRECC studies, this in-house developed

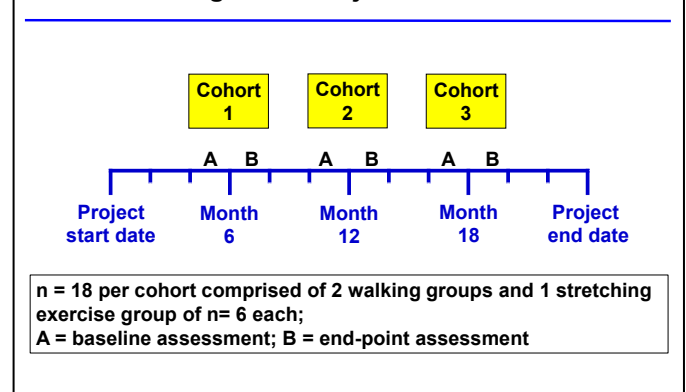| Table 2: Assessment Schedule		
Domain/Test	**Baseline**	**End-point**
Sample characterization		
SCID	X	
Psych and Social History	X	
BMI	X	X
Smoking behavior	X	X
Cardiorespiratory fitness		
Rockport one-mile walk test	X	X
Cognition		
Non-social cognition battery	X	X
Social cognition battery	X	X
Neurotrophic factor		
BDNF	X	X
Affect and symptoms		
PANAS	X	X
BPRS	X	X
Motivation	X	X
Social Integration		
Birchwood Social Functioning Scale	X	X
TSBC	X	X

instrument is used to collect data on demographics, psychiatric history, and current medications. We will also measure BMI and current and past smoking behavior. Administration time is 20 minutes.

C.5.3 Cardiorespiratory fitness. Cardiorespiratory fitness will be measured using the Rockport one-mile walk test that provides an estimate of maximal oxygen consumption ($VO_{2 max}$)[44]. This non-invasive procedure uses a regression-based formula that includes age, sex, weight, time to walk one-mile, and heart rate after one-mile as variables. Heart rate will be measured using a Fitbit ChargeHR heart rate monitor worn by the Veteran. This method correlates .93 with direct measurement of $VO_{2 max}$. Time is about 20 minutes for most individuals.

C.5.4 Cognition. Selected areas of non-social and social cognition will be assessed: (a) Non-social cognition: attention (CPT-IP), speed of processing (BACS symbol coding), working memory (WAIS-IV letter-number sequencing test), verbal learning (Hopkins Verbal Learning Test – Revised), and executive control (AX-CPT)[45, 46]. (b) Social cognition: emotion perception (Facial Emotion Identification Test[47]), social perception (Half-Profile of Nonverbal Sensitivity; PONS[48]), theory of mind (The Awareness of Social Inference Test; TASIT – Part 2[49]), empathy (empathic accuracy test[50]). For both non-social and social cognition, the primary measure will be an overall composite. Total administration time is approximately 90 minutes.

C.5.5 Neurotrophic factor (BDNF quantification). To assess possible brain-related changes consequent to PE, serum will be collected on the same day as the baseline and end-point assessments and stored at -80 C to measure BDNF. BDNF concentration remains relatively stable within an individual's system for up to 2 weeks and will be quantified by enzyme-linked immunosorbent assay (R&D Systems) with assay range of 62.5-4000 pg/ml. Assays will be performed by the UCLA Clinical and Translational Research Laboratory.

C.5.6 Affect and psychiatric symptoms.

(a) Positive and negative affect. Affect will be measured using the Positive and Negative Affect Schedule (PANAS) [51], a self-report measure tapping 20 different feelings requiring 5 minutes administration time. The primary measures will be total scores for positive affect and negative affect.

(b) Clinical symptoms. Positive and negative symptoms will be assessed using the Expanded Brief Psychiatric Rating Scale (BPRS)[52]. Primary measures are positive and negative symptom subscale scores. Administration time is 25 minutes.

(c) Motivation. Motivation will be measured using the Effort Expenditure for Rewards Task [53], a computerized measure developed out of the affective neuroscience literature[54] in which the participant chooses easy or hard button-pressing tasks for variable amounts of reward. In schizophrenia, it has shown good test-retest reliability (r=.73) and small practice effects (d=.09). The primary measure will be the percent of hard choices across reward levels. Administration time is 25 minutes.

C.5.7 Social integration. Social integration will be assessed with 2 measures with established reliability and validity in schizophrenia and serious mental illness [55-57]: (a) Birchwood Social Functioning Scale [55]: This measure is administered as a structured interview and includes 7 subtests which assess social engagement, interpersonal communication, independence – performance, independence – competence, recreation, prosocial behavior, and employment, and yields a total score. (b) Time Sample Behavior Checklist (TSBC)[58]: This behavioral observation measure assesses frequency of involvement in common human behaviors such as talking, reading, etc. Behavior samples will be drawn from a 5-min observation period of Veterans gathered in the waiting area immediately after the first and last session. A rater trained to a kappa = .90 with the PI will sample the behavior of each Veteran within the respective group in semi-random 2-sec windows conducted 2 times per min yielding a total of 10 observations. The primary variable is percent time engaged in prosocial behavior, e.g., talking to others. These 2 measures require 20 minutes administration time. The primary measure for social integration will be an overall composite derived from these 2 measures.

C.6 Quality assurance

For the walking and stretching exercise groups, the PI will observe each group 1 day per week to monitor implementation. The PI and co-investigators will monitor the collection of cardiorespiratory fitness and BDNF data. Each month, the PI will meet with the tester and study coordinator to review data collected. Symptom ratings will be carried out by an interviewer trained to reliability (i.e., kappa > .80).

D. Data Analytic Plan

C.3.1 Statistical Analysis Approach

C.3.1.1 Specification of primary measures. Our primary outcome variables will be the estimated $VO_{2 max}$ value from the Rockport one-mile walk test (Hypothesis 1), a composite score of non-social cognition (Hypothesis 2), and total scores from the PANAS for positive and negative affect (Hypothesis 3).

C.3.1.2 Preliminary analyses. Descriptive statistics and graphical summaries on all demographic, clinical and outcome measures will be examined to characterize the sample, to determine the advisability of scale transformations or non-parametric methods and to identify missing values, outliers, or other features that may be influential. To assess tolerability, attendance and dropout rates will be compared for the two study arms; within the exercise group session-by-session heart rate data will be plotted to examine whether exercise targets were consistently achieved over time. To verify the success of randomization, we will compare

treatment groups at baseline on all primary outcome measures, as well as demographic and clinical factors. Measures that show significant group differences and are correlated with the primary outcome measures will be included as covariates in follow-up analyses to verify the robustness of observed effects.

Table 3. Aim x Hypothesis x Outcome Measure x Analysis.			
Specific Aim	Hypothesis	Outcome Measure(s)	Statistical Analysis
To examine the benefits of physical exercise on cardio-respiratory fitness, cognition, and affect in Veterans with schizophrenia.	Hyp 1: Veterans in the exercise group will show greater improvement in physical fitness as measured by a cardiorespiratory measure of functioning compared to a control group.	Estimate of $VO_{2\ max}$ from Rockport one-mile walk test	Mixed effects regression with group, time, and a group x time interaction.
	Hyp 2: Veterans in the exercise group will show greater improvement in cognition compared to a control group.	Primary: Composite score from non-social cognition battery Secondary: Composite score from social cognition battery; BDNF value	Mixed effects regression with group, time, and a group x time interaction.
	Hyp 3: Veterans in the exercise group will show greater increases in positive affect and greater decreases in negative affect compared to a control group.	Primary: Total scores on positive affect and negative affect from the PANAS. Secondary: Positive and negative symptom subscale scores from the BPRS	Mixed effects regression with group, time, and a group x time interaction.

C.3.1.3 *Primary analyses by hypothesis* (see Table 3 above): The primary analyses are all intent-to-treat with subjects grouped as randomized to the PE or control conditions. We will use generalized linear mixed models (GLMMs) with treatment group as the between subjects factor, time as the within subjects factor, and a group x time interaction as the primary predictors, along with subject and cohort level random effects to account for correlations induced by repeated measurements within subjects and shared group experiences. GLMMs allow for both fixed and time-varying covariates and automatically handle missing data, producing unbiased estimates as long as observations are missing at random. Our primary hypotheses regarding the efficacy of PE correspond to tests of the group x time interactions for differential effects of treatment on cardiorespiratory fitness, non-social cognition, and positive and negative affect. A significant interaction effect in the predicted direction would support the hypothesis that PE is an effective training intervention for improving one or more of these areas of functioning. Post-hoc contrasts can be used to assess the degree of improvement within the exercise group. Follow-up analyses will adjust as necessary for demographic and clinical covariates. In addition, where treatment effects are observed on composite outcome measures, secondary analyses will be run for the individual component domains to determine whether particular factors are driving the overall results.
C.3.1.4 *Exploratory analyses:* Our ultimate goal is to determine whether the benefits of PE extend to improvements in social integration in Veterans with schizophrenia. We will conduct exploratory analyses, using the same GLMM paradigm as in the primary analyses, to obtain initial estimates of the effects of PE on social integration. We will also examine changes in social cognition, BDNF, and symptoms to see if these areas are sensitive to the effects of training. Our overall conceptual view is that any observed PE related improvements in social integration will be the result of improvements in non-social cognition and affect. If this study is successful, a natural next step is to test the effects of PE on social integration with inclusion of non-social cognition and affect as mediators. While we are underpowered for the full path analysis here, we will conduct exploratory analyses to examine whether non-social cognition and affect mediate the effect of treatment on social integration outcomes by including these measures as time-varying covariates in the GLMMs for social integration. In addition, we will add baseline clinical and contextual factors (BMI, smoking behavior, symptoms, and motivation) and their interactions with group and time to the primary mixed models to begin exploring potential moderators of treatment effects. We also plan to examine cohort effects to see if there are any significant changes in the PE training program over time (comparing cohort 1 vs. 2 vs. 3).
C.3.2 Power
We plan to enroll 54 subjects, 36 in the experimental treatment arm and 18 in the control arm. All sample size calculations are based on a 2-sided significance level of $\alpha=.05$, and assume a correlation of $r = .5$ between repeated measurements within subjects. We allow for 17% attrition based on data from 2 ongoing studies that yielded 15.9% and 16.7% attrition rates, respectively (Young: 44/276 lost at 6-mo follow-up; Kern: 7/42 lost at end-point following a 3-mo psychosocial training intervention). For each of our hypotheses, our design has 80% power to detect an interaction with effect size of $f = .21$ (the general effect size unit for ANOVA/regression) which translates to a change from no difference at baseline to a difference of $d = .85$ SDs at the endpoint. Within the exercise group there is 80% power to detect an improvement of $d = .5$ on any of the outcome measures, a standard medium effect. From the literature, the 2 RCTs on cognition examining PE alone vs. a control condition yielded effect sizes of $f = .59$[26] (for the interaction) and $d = .93$[27] (for between-group comparison of change scores); the one on affect reported a medium effect for within-group change (no control condition; $d = .66$) [29], so power should be adequate for cognition and based on the limited data on affect we should be able to obtain reasonable estimates to inform a future study.