Grant Report

Improving Cognition via Exercise (ICE): Study Protocol for a Multi-Site, Parallel-Group, Single-Blind, Randomized Clinical Trial Examining the Efficacy of Aerobic Exercise to Improve Neurocognition, Daily Functioning, and Biomarkers of Cognitive Change in Individuals with Schizophrenia †

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ABSTRACT

Individuals with schizophrenia (SZ) display cognitive deficits that have been identified as major determinants of poor functioning and disability, representing a serious public health concern and an important target for interventions. At present, available treatments offer only minimal to moderate benefits to ameliorate cognitive deficits. Thus, there remains an urgent need to identify novel interventions to improve cognition in people with SZ. Emerging evidence from animal and basic human research suggests aerobic exercise training (AE) has beneficial effects on cognition. Preliminary findings suggest that AE is efficacious in improving cognitive functioning in SZ, however the extant studies have been limited by small samples, a dearth of information on biologically-relevant covariates, and limited information on impact on daily functioning. Additionally, while AE-related cognitive benefits have been linked to Brain-Derived Neurotrophic Factor (BDNF) upregulation, this putative mechanism needs

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confirmation. The present report describes a study protocol designed to address these limitations—we review and summarize the current literature on treatment of cognitive deficits in SZ, state the rationale for employing AE to target these deficits, and describe the current protocol—a multi-site, single-blind, randomized clinical trial aiming to recruit 200 community-dwelling individuals with SZ. Participants are randomized to one of two 12-week interventions: AE using active-play video games (*i.e.*, Xbox Kinect) and traditional cardiovascular exercise equipment or a stretching-and-toning (ST) control intervention. Participants undergo assessments of aerobic fitness, cognition, and daily functioning, as well as BDNF and other biomarkers of cognitive change, at baseline and after 6- and 12-weeks.

KEYWORDS: schizophrenia; cognition; functioning; aerobic exercise; aerobic fitness; BDNF; neurotrophins; inflammation; neuroplasticity

BACKGROUND

Individuals with schizophrenia (SZ) display a broad range of neurocognitive deficits across multiple domains including processing speed, attention, executive functioning, verbal and visual memory, and social cognition [1–5]. An estimated 90% of individuals with SZ show impairment in at least one neurocognitive domain, and 75% are impaired in at least two [6]. These deficits have been identified as major determinants of poor functioning and disability [2,7], representing a serious public health concern and an important target for interventions [8,9].

Currently available treatments for cognitive deficits in SZ have centered on two primary modalities—pharmacotherapy and cognitive remediation (CR) [10,11]. First and second- generation antipsychotics that were developed to target psychosis have exhibited limited efficacy in improving cognition in SZ [12]. Similarly, results from the Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) initiative, a collaboration between NIMH, academia, FDA, and the pharmaceutical industry aimed at stimulating new drug development to target poor cognition in SZ, have been disappointing [13,14]. Meta-analytic studies assessing the efficacy of CR have provided more promising results, demonstrating benefits of medium effect size [10,15,16], although one recent large, NIMH-sponsored trial of 166 SZ patients undergoing 120 CR training hours over 6 months reported no cognitive benefits [17]. While the CR literature has been criticized on a number of methodological grounds [10,15,16], benefits were evident primarily in studies in which CR was accompanied by psychiatric rehabilitation [18,19]. Yet, there remains an urgent need to identify novel approaches for the development of treatments targeting cognitive deficits in SZ [20,21].

Effective cognitive functioning is related to the brain's ability to modulate neural connectivity and function. Such neuroplasticity is dependent on the contributions of neurotrophins, a family of proteins that signal neurons to survive, differentiate, and grow [22,23]. Among neurotrophins, Brain-Derived Neurotrophic Factor (BDNF) is particularly relevant to such processes given its abundance in the CNS [24], and its many neurotrophic and neuroprotective properties including axonal and dendritic growth, neuronal protection and survival, neuronal differentiation, synaptogenesis and efficacy in synaptic transmission [25,26]. Individuals with SZ have been shown to exhibit lower levels of serum-BDNF compared to healthy controls [27,28], which has been linked with poor short-term memory [29] and smaller hippocampal volume [30]. Furthermore, in a recent meta-analysis of SZ studies, Ahmed *et al.* [31] found higher peripheral BDNF levels significantly correlated with better performance on reasoning and problem-solving tasks. Thus, BDNF upregulation may lead to improvements in cognitive functioning and may serve as a promising target for interventions.

One activity that is known to upregulate BDNF and improve cognitive functioning is aerobic exercise training (AE) [32–35], with synthesis and release of BDNF into blood circulation occurring in a dose-response manner [36,37]. Consistent with these findings, a recent meta-analysis of 29 studies demonstrated increases in BDNF after a single bout of exercise [38]. Likewise, animal research strongly supports the positive influence of AE on cognitive functioning [39], along with increases in cell proliferation and survival, particularly in the dentate gyrus [40–42]. AE has also been linked to new blood vessel growth in the motor cortex [43], the cerebellum [44], the hippocampus [45], and the striatum [46]. In humans, an extensive literature supports the beneficial impact of AE on cognition in adolescents, young adults, and older adults [47–50]. In a meta-analysis of 29 RCTs (n = 2021), AE significantly improved attention, processing speed, executive functioning, and long-term memory, with a trend for working memory [51]. Similarly, imaging studies indicate that AE-related cognitive improvements are mediated by structural and functional brain changes [52–54]. In summary, extensive literatures on animal and human research converge in supporting the positive influence of AE on cognition [33,35,55–57], pointing to robust benefits across the mammalian lifespan [33,34,56,58–60].

Germaine to SZ, individuals with SZ tend to be highly sedentary, displaying significantly lower rates of physical activity and fitness compared to healthy individuals [61]. For example, individuals with SZ have been found to spend up to 81% of their wake time in sedentary behavior, and 98% of SZ patients have been found to exhibit age-adjusted low aerobic fitness [62]. A burgeoning research literature suggests that, along with aerobic fitness (AF), AE also improves cognitive functioning in people with SZ. A pilot RCT from our group (n = 33) demonstrated that a 12-week AE training program improved VO_2max-indexed aerobic fitness

by 18% in individuals with SZ, compared to a minimal change in the Treatment-As-Usual (TAU) control participants. The enhancement in aerobic fitness was accompanied by a 15.1% improvement in cognitive functioning (vs −2.0% decline in the TAU group). Hierarchical multiple regression analyses indicated that enhancement in aerobic fitness and upregulation of BDNF predicted 25.4% and 14.6% of the neurocognitive improvement variance, respectively. Most notably, the 12-week AE intervention eliminated 24% of the cognitive functioning deficit in the SZ group (when compared to healthy controls' standardized scores). Consistent with our findings, a number of recent reviews and meta-analyses indicate that AE training is effective in increasing VO_2max-indexed aerobic fitness in individuals with SZ [63–67], with VO_2max improvements ranging from 8 to 38%, and such interventions leading to cognitive benefits. Specifically, a recent meta-analysis of 10 trials (n = 385 individuals with SZ) found AE significantly improved global cognition (g = 0.33), with a higher effect size in the 7 included RCTs (g = 0.43) [68]. Meta-regression analyses further indicated that AE significantly improved the cognitive domains of working memory, social cognition, and attention/vigilance [68].

More recently, a number of studies examined the efficacy of AE in improving aspects of daily functioning in people with SZ. Two RCTs that utilized 120-min per week of moderate-to-vigorous AE training observed significant improvements in functional disability and quality of life, as well as reductions in need for care [63,64]. Firth and colleagues [69] also reported improved social functioning for 31 patients in response to a 10-week AE intervention, while some RCTs using low-intensity AE compared to a yoga intervention reported increases in social functioning [70,71]. In another study, Lee *et al.* [72] discovered that physical activity among first-episode SZ patients predicted better functioning 6 months later, while one meta-analysis found a moderate influence of physical activity on quality of life [73]. Finally, in results from our recent pilot RCT [74], patients with SZ who completed the AE intervention improved their daily functioning, as indexed using the informant-based Specific Level of Functioning Scale (SLOF), compared to participants in the TAU control group. These improvements in daily functioning were driven primarily by improvements in the SLOF Work Skills domain.

While converging lines of preclinical and clinical research strongly support the scientific premise of employing AE to improve cognitive functioning in people with SZ, the literature also has a number of significant limitations: (1) a number of biological variables such as sex, age, and BMI may be relevant to changes in aerobic fitness, but have been largely unconsidered as covariates in existing studies due to small sample sizes. A recent meta-analysis [75] indicated that among people with SZ, increased BMI and female gender were negatively associated with AF (indexed by VO_2max). However, there are no publications indicating sex, age, or BMI have a moderating effect on the ability to improve AF among

people with SZ attending AE training. Among healthy individuals, Sloan and colleagues investigated sedentary young adults (n = 149; age = 30.4 ± 7.53 years) randomized to receive 12 weeks of AE followed by 4 weeks of sedentary deconditioning [76]. They found men and women did not differ in their ability to increase aerobic capacity after training and decrease capacity after deconditioning. Likewise, BMI and age did not affect the findings; (2) previous investigations tended to center on the impact of AE on a single or limited range of cognitive domains (*i.e.*, memory), thus leaving a need for a comprehensive examination of cognitive functioning across multiple domains; (3) information about the impact of AE on daily functioning is limited to self-reports and/or ratings by clinicians with infrequent contact with patients, rather than from objective (laboratory) tasks or informants who engage patients regularly in the "real world"; (4) previous reports have linked BDNF and cognition, BDNF and AE, and AE and cognition in SZ, however there is a need for a sufficiently powered study to link all three variables, confirming the putative role of BDNF as a biomarker of AE-related cognitive change; and (5) previous AE studies in SZ tend to view AE as a uniform intervention, with limited attention given to intervention characteristics. Specifically, previous studies often limited characterization to crude measures (*i.e.*, attendance). Such lack of data has critical implications for reproducibility, as studies may report similar attendance, but different results due to distinct in-session behaviors (e.g., training intensity). Preliminary evidence from our pilot [74] suggests that cognitive improvement is highly correlated with AE training intensity.

Altogether, these limitations hinder our ability to make informed decisions regarding the efficacy of AE to ameliorate cognitive deficits in people with SZ. To address this very specific need, the proposed study focuses on three major aims—AIM 1: confirm the efficacy of AE training to improve cognition in people with SZ; AIM 2: examine the impact of AE on daily functioning; and AIM 3: examine BDNF and other biomarkers as AE-related indicators of cognitive-change. We plan to examine closely the impact of potentially relevant biological variables including sex, age, and BMI, as well as quantify intervention delivery and assess their impact on outcomes. Findings from the present study can help inform health policy decisions regarding the use of AE as a standard therapeutic modality for cognitive deficits in people with SZ. If confirmed, the results will help to transition the field from efficacy testing to examining the "real-world" effectiveness of AE in addressing cognitive deficits in SZ in various clinical settings. To help with data interpretation and to encourage replication, we provide a detailed description of the methodology and interventions employed in the trial.

METHODS

The study employs a multi-site, parallel-group, single-blind, randomized, clinical trial design (Figure 1). Participants are randomized to one of two 12-week, 3 times per week, 1-hour interventions: (1) AE

training using active-play video games (*i.e.*, Xbox Kinect) and traditional exercise equipment; or (2) a stretching and toning (ST) control intervention. All participants continue to receive their ongoing psychiatric and medical treatment during the 12-week interventions. Assessments of clinical, neurocognitive, and functioning measures, as well as collection of biomarkers, are completed at the start of the trial (baseline, T_0), and after 6- and 12-weeks of the interventions (T_1 and T_2, respectively).

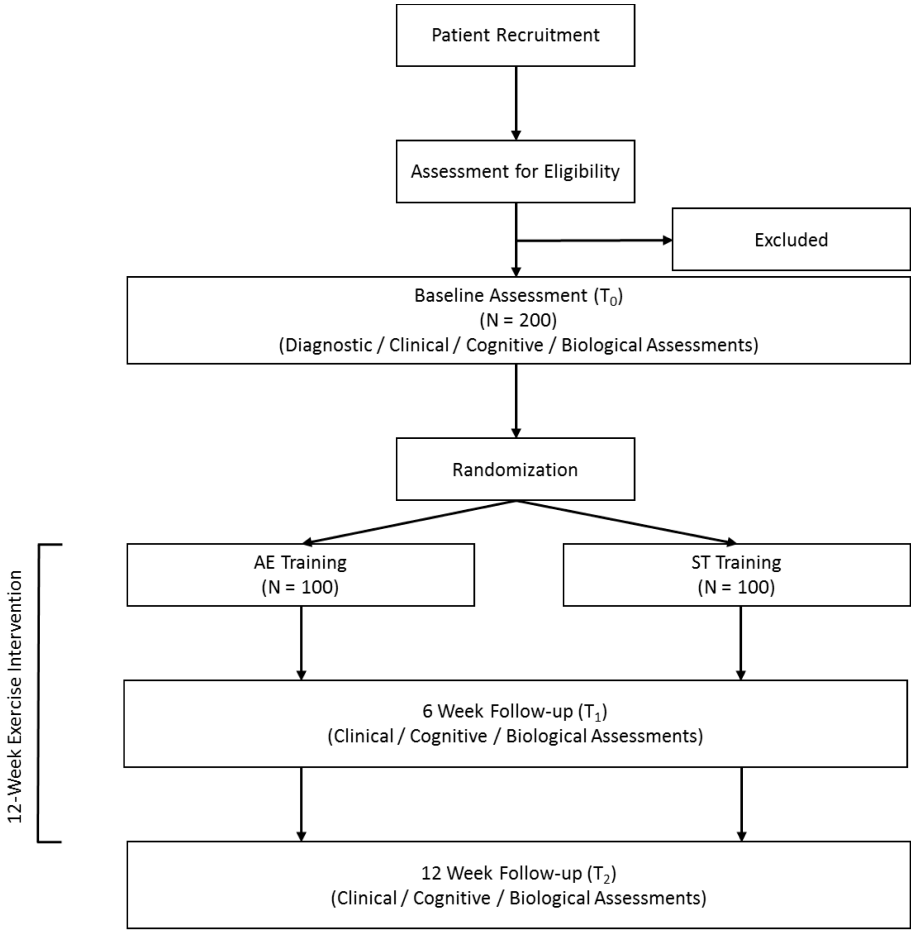

Figure 1. Flow chart—Participants in the Improving Cognition via Exercise (ICE) in schizophrenia trial. Note: AE: Aerobic Exercise; ST: Stretching-and-Toning.

Recruitment and Eligibility

Recruitment began in April 2018. Two hundred outpatients diagnosed with SZ and related disorders will be recruited from four geographically and demographically diverse U.S. sites: The Icahn School of Medicine at Mount Sinai (New York), University of North Carolina at Chapel Hill (North Carolina), Stanford University (California), and Augusta University (Georgia). The inclusion and exclusion criteria are presented in Table 1. Criteria for termination from the study include: (1) a clinical adverse event, abnormal laboratory results, or clinical deterioration which, in the opinion of the study PIs, suggests that continued participation is not in the participant's best interest; (2) pregnancy; or (3) participant withdraws

consent. If worsening psychiatric symptoms results in a hospitalization, a participant may elect to continue study participation after discharge from the hospital if: (1) the hospitalization was brief (14 days or less); (2) the individual is interested and re-signs the consent form; and (3) the participant's treating psychiatrist agrees to their continued participation. In such cases, the participant will continue to receive their previously assigned intervention.

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria
Age between 18–55
DSM-IV diagnosis of schizophrenia, schizoaffective, or schizophreniform disorder
Taking antipsychotic medication for at least 8 weeks and on current doses for 4 weeks, and/or injectable depot antipsychotics for 3 months
Medical clearance by a physician to complete VO_2max and AE/ST training
Capacity to understand risks and benefits of the study
Exclusion Criteria
DSM-IV diagnosis of substance use disorder (except nicotine) within the past month or diagnosis of substance dependence (except nicotine) within the last 6 months
Initiation of antidepressants, mood stabilizers or other medications known to impact cognition in previous 4 weeks, or any change in medication dosage during this period
History of seizures/head trauma with loss of consciousness greater than 10 min resulting in cognitive sequelae
Significant clinical abnormalities in physical examination, laboratory assessments, or ECG that would affect study participation
Neurological or medical conditions that could interfere with study participation
BMI ≥ 40
Untreated hyper- or hypothyroidism
Pregnant and/or nursing
Serious homicidal or suicidal risk within the last 6 months *
"Moderate" or more severe conceptual disorganization (PANSS ≥ 4)
Poor English reading ability (WTAR < 7)
Participation in a study with cognitive assessment in the past 3 months

Note: DSM: Diagnostic and Statistical Manual of Mental Disorders; VO_2max: maximal oxygen uptake; AE: Aerobic Exercise; ST: Stretching and Toning; BMI: Body Mass Index; PANSS: Positive and Negative Syndrome Scale; WTAR: Wechsler Test of Adult Reading. * Suicidal risk is no longer an exclusion criterion as of October 2019, given award of an NIH supplemental grant assessing the influence of exercise on suicide risk in schizophrenia (PIs: Kimhy & Stroup).

Procedures established to minimize study attrition include: (1) providing compensation for transportation to exercise sessions (weekly) and research assessments (upon completion); (2) follow-up contact (via phone or email) after missed exercise sessions; and (3) weekly assessment of exercise-related adverse events/side effects, as well as inquiry about study-related challenges.

INTERVENTIONS

The AE and ST interventions are conducted at local site-affiliated exercise facilities, are held in small groups (typically 3–4 participants/group), and are led by a certified exercise trainer who is present during all training sessions. To ensure quality of interventions, we hired exercise trainers certified by the following organizations: the American College of Sports Medicine (ACSM), the National Strength and Conditioning Association (NSCA), or the American Council on Exercise (ACE). Additionally, a research assistant is also present to set-up and collect exercise-related equipment (e.g., heart rate (HR) monitors) and record exercise-related behavioral data. During all exercise sessions, participants are encouraged to hydrate and take breaks as needed.

Aerobic Exercise (AE)

The AE intervention is informed by federal and ACSM guidelines (American College of Sports Medicine; *2008 Physical Activity Guidelines for Americans*), which recommends 150 min of moderate-intensity AE per week across 3 days. Such activities expend 3 to 5.9 times the energy expended at rest and are defined as activities in which the individual is able to talk while engaging in the activity. We elected to employ a 3 times per week AE training intervention based on the following factors: (1) our pilot RCT [74,77–79] that demonstrated efficacy of 3 times per week AE to significantly improve aerobic fitness and cognition in individuals with SZ; (2) a recent meta-analysis of 20 AE RCTs in SZ that indicated interventions which used less than 90 min per week of any moderate-to-vigorous AE failed to improve psychiatric symptoms, functional disability, or cognition [65]; (3) similar findings in studies of depression and other mental health samples [80,81]; and (4) federal and ACSM guidelines.

AE sessions open with a 10-minute trainer-led warm-up period, after which participants exercise for 45 min using the AE equipment, and end with a 5-min cool-down period. Similar to our pilot study [74,77–79], participants are free to choose which AE equipment and exercise activity they wish to use, with encouragement from the trainer to change equipment every 15–20 min to allow all participants to use all exercise equipment, as well as diversify physical exercise routines. All sites are equipped with identical equipment including a treadmill, stationary bicycle, elliptical machine, and an *Xbox* video-game console with a *Kinect* motion-sensing device that runs interactive whole-body fitness activity software. The American Heart Association has recommended the *Xbox Kinect* and similar devices as tools for promoting physical activity [82]. Studies with healthy individuals suggest whole-body exercises using such devices can stimulate moderately intense aerobic activity in adults, with enjoyment rated significantly higher than traditional exercises [83,84], thus representing a comparable fitness alternative [85,86]. Results from our pilot study suggest feasibility and safety among individuals with

SZ [74]. The AE equipment was selected based on its ease of use and maintenance, limited storage space, and affordability, all contributing to broad dissemination in the event of positive trial results.

Initial AE training intensity is set for each participant individually based on his/her maximal and resting HR (*i.e.*, using the Karvonen formula) [87] as determined during their baseline VO_2max test, with intensity set to 60% of max HR in Week 1, 65% in Week 2, 70% in Week 3, and 75% in Weeks 4–12. AE training fidelity is indexed by: (1) the number of sessions a participant attended; and (2) in-session training intensity recorded as the number of minutes per session participants trained with their HR at or above their designated weekly training intensity. Training intensity was included to address the possibility that participants will attend training sessions, but exercise lightly. In-session AE intensity is monitored using HR monitors that participants wear during sessions. Monitors are programmed to emit a soft beep when a participant's HR is lower than the designated, individually-specified weekly AE intensity level, adjusted for the specific training week. If a participant's HR falls under their target HR intensity level, the exercise trainer is instructed to encourage the participant to achieve their target goal. At the end of the session, the research assistant uploads the data from the HR monitors to both a computer and the study's data management system for processing and review.

In addition to serious adverse events (SAE), we monitor on a weekly basis potential AE-related minor and moderate adverse events including musculoskeletal/soft tissue (muscle soreness, muscle pull/strain, joint pain, falls); cardiovascular (fatigue, dyspnea, chest pain that resolves with rest); and skin-related side-effects (blisters, chafing). Previous studies indicate a minimally small risk of adverse events as part of AE-related interventions [74,88]. Our screening procedure, the use of a "start low and go slow" strategy, close monitoring of AE intensity, and the presence of a certified exercise trainer aims to minimize the risk of adverse events.

Stretching and Toning (ST)

ST exercises involve static stretching—a series of techniques that gradually lengthen a muscle to an elongated position to the point of tightness or discomfort and maintenance of that position for 30 to 60 s. ST exercises are recommended by the ACSM guidelines (*2008 Physical Activity Guidelines for Americans*) to improve flexibility [89]. We chose ST as a control intervention as it does not affect aerobic fitness while holding other variables such as schedule, duration, facilities, format, (e.g., indoor space; small group), trainer contact, social interactions, and financial payments (*i.e.*, reimbursement of exercise travel expenses) as similar as possible to the AE training program. The ST group performs trainer-supervised stretching exercises using a schedule and duration similar to the AE group. ST training intensity is set for each participant individually based on his/her maximal and resting HR (*i.e.*, using the Karvonen

formula) [87] as determined during their baseline VO_2max test, with intensity set under 60% in Weeks 1–12. We measure ST training fidelity using: (1) the number of sessions attended; and (2) in-session training intensity recorded as the number of minutes per session participants trained with their HR below their designated training intensity. The monitors are programmed to emit a soft beep when participant's HR is higher than the individually-specified weekly AE intensity level. If a participant's HR is above their target HR intensity level, the exercise trainer is instructed to encourage him/her to achieve their target goal. Similar to the AE intervention, at the end of the session, the research assistant uploads the data from the HR monitors to a computer and the data management system for processing and review. ST exercises are low impact and present minimal risk for injury. We utilize a monitoring strategy similar to the one used for the AE training program.

Monitoring interventions' delivery and fidelity

A major strength of our protocol is the use of a data management system that allows for near real-time, dynamic monitoring of study participants' attendance and in-session training intensity. We monitor participants in both intervention arms using this system. Within 24 h of a completed AE or ST session, site personnel enter data into the data management system indicating whether a participant attended their scheduled session, and if so, upload the participant's in-session HR data collected via HR monitors. Additionally, for AE participants, personnel enter the number of minutes each participant exercised at or above their designated weekly target intensity (60 to 75% of maximal HR). For ST participants, we monitor the number of minutes each participant exercised below 60% of their maximal HR. After uploading to the online database, personnel at Icahn School of Medicine at Mount Sinai monitor the data for inconsistencies. The system allows for granular examination of intervention fidelity (see Figure 2—a participant's weekly report of training attendance and intensity). Such reporting allows us to address specific sites in nearly real-time if a trainer and/or a participant are not meeting their target training intensity. In the absence of this system, such situations may not be recognized until end-of-study or at all.

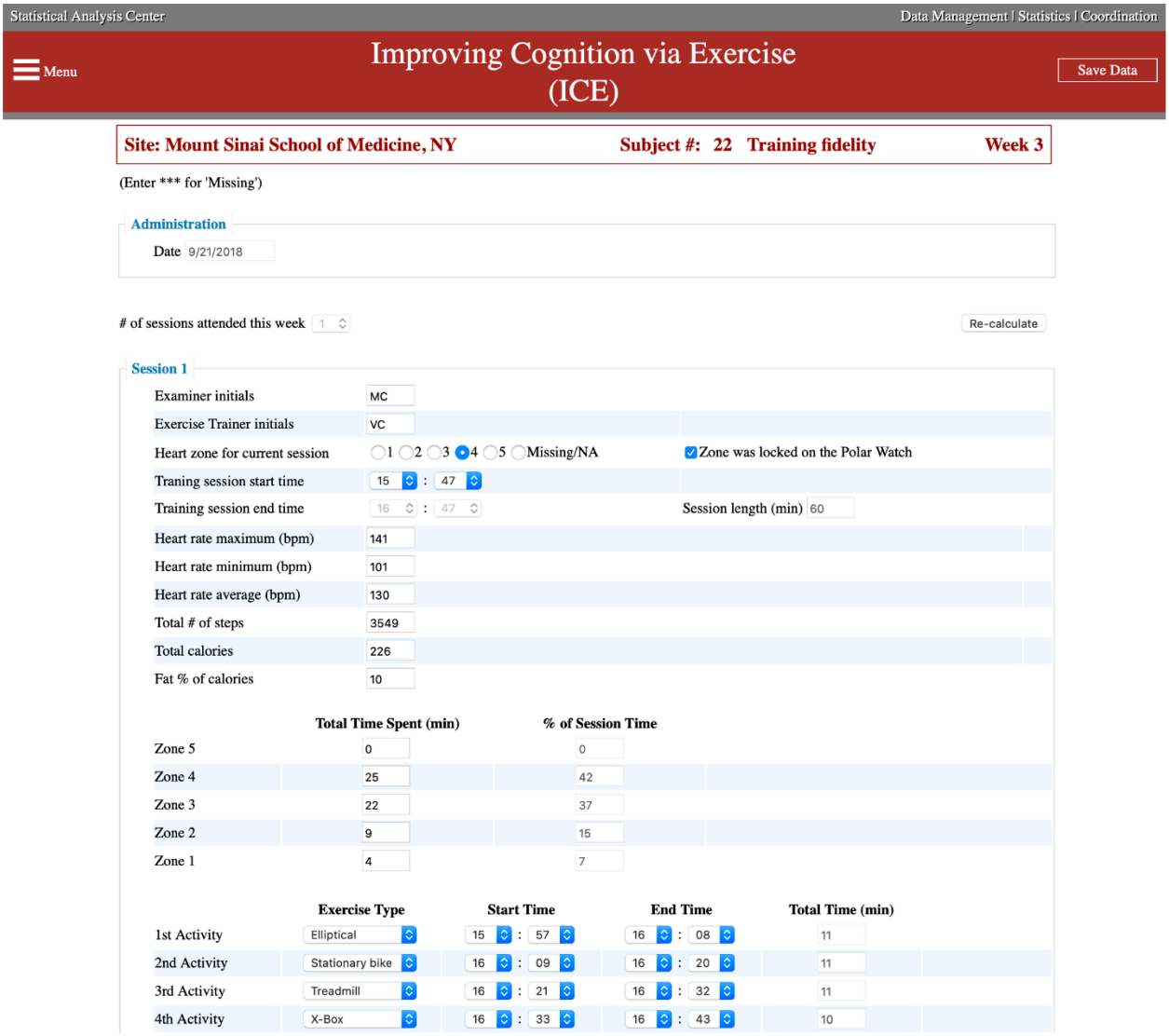

Figure 2. Sample screen shot of participant's fidelity exercise training data.

The data management system generates reports relating overall and site-specific progress of recruitment, completion of assessments, intervention attendance, and in-session intervention fidelity. These data are shared and reviewed with all site PIs during bi-weekly conference calls attended by the overall study and site PIs. Review of reports allow timely response in the event of deviation from recruitment, shortcomings in intervention goals, and/or delays in research assessments.

EXPERIMENTAL DESIGN

Participants are assessed at three time points: baseline, intervention midpoint (*i.e.*, 6 weeks), and end-of-study upon completion of the intervention (*i.e.*, 12 weeks). The schedule of assessments at all three time points are outlined in Table 2. After completing the initial phone screen and satisfying initial inclusion/exclusion criteria, participants complete baseline assessment over three visits. On Visit 1, participants complete diagnostic, demographic, medical, and clinical assessments, as well as a

toxicology test. On Visit 2, following overnight fasting, participants provide a blood sample, followed by completion of neurocognitive and behavioral assessments. At the end of the visit, participants be provided with an Actigraph monitor to wear for a week to measure baseline levels of physical activity. On Visit 3, participants return the activity monitor, and complete an aerobic fitness (VO_2max) test followed by daily functioning and behavioral assessments. The baseline assessment battery is typically completed in 8 hours, over 3 visits. Following the completion of baseline assessment and fulfilling medical clearance, participants are randomized consecutively in the order they enter the study at their site to either the AE or ST interventions (stratified by site) and begin their assigned exercise training program within a week of randomization.

Table 2. Assessment schedule in the Improving Cognition via Exercise (ICE) in schizophrenia trial.

Assessments	**Baseline** T_0	**Training Sessions Weeks 1–6**	**6-Week** T_1	**Training Sessions Weeks 7–12**	**12-Week** T_2
Phone Screen	PreV				
Informed Consent	RV1				
Contact Information	RV1				
Demographics	RV1				
Urine Toxicology/Pregnancy Screen	RV1		RV4		RV6
Medications	RV1		RV4		RV6
Wechsler Test of Adult Reading	RV1				
Structured Clinical Interview for DSM-IV Axis I Disorders	RV1				
Positive and Negative Syndrome Scale	RV1		RV4		RV6
Beck Depression Inventory	RV1		RV4		RV6
Childhood Trauma Questionnaire	RV1				
Suicide Risk Assessment	RV1		RV4		RV6
Clinical Global Impression	RV1		RV4		RV6
Medical History/Physical Exam	RV1				
Blood Collection and Analyses	RV2		RV4		RV6
MATRICS Consensus Cognitive Battery	RV2		RV4		RV6
Additional Clinical Information	RV2		RV4		RV6
Pittsburgh Sleep Quality Index	RV2		RV4		RV6
Fagerström Test for Nicotine Dependence	RV2		RV4		RV6
International Physical Activity Questionnaire	RV2		RV4		RV6
Beck Anxiety Inventory	RV2		RV4		RV6

Table 2. *Cont.*

Assessments	Baseline	Training Sessions	6-Week	Training Sessions	12-Week
	T_0	Weeks 1–6	T_1	Weeks 7–12	T_2
Toronto Alexithymia Scale-20	RV2				RV6
Actigraph (7 days)	RV2				RV6
VO_2max	RV3		RV5		RV7
UCSD Performance-Based Skills Assessment	RV3		RV5		RV7
Schizophrenia Cognition Rating Scale (participant/informant)	RV3		RV5		RV7
Specific Levels of Functioning (informant only)	RV3		RV5		RV7
Emotion Regulation Questionnaire	RV3				RV7
Satisfaction with Life Scale	RV3				RV7
Inclusion/Exclusion Criteria	RV3				
Training Fidelity		EV *		EV *	
Adverse Events/Side Effects		EV **		EV **	

Note: T_0: Baseline; T_1: 6-Week; T_{12}: 12-Week; PreV: Pre-Visit; RV: Research Visit; EV: Exercise Visit; * per session; ** weekly.

Following the 6-week midpoint of exercise training sessions (T_1), participants complete research assessments over a two-day period (*i.e.*, Visits 4 and (5) to determine how early the impact of AE training may manifest on cognition and functioning. On Visit 4, following overnight fasting, participants provide a blood sample, followed by completion of neurocognitive and behavioral assessments; on Visit 5, participants complete an aerobic fitness (VO_{2max}) test followed by daily functioning and behavioral assessments. Finally, at end-of-study following 12 weeks of training sessions (T_2), participants complete research assessments over a two-day period (*i.e.*, Visits 6 and 7). On Visit 6, following overnight fasting, participants provide a blood sample, followed by completion of neurocognitive and behavioral assessments; they are also provided with an Actigraph monitor to wear for a week to measure end-of-study levels of physical activity. On Visit 7, participants return the activity monitor, and complete an aerobic fitness (VO_2max) test followed by daily functioning and behavioral assessments. The 6- and 12-week assessment batteries are typically completed in 7 h over 2 visits, each.

Blinding Procedures

Assessments of aerobic fitness, cognition, daily functioning, psychiatric symptoms, and biomarkers analyses are performed by research staff blinded to the participant's randomization status. Fidelity of blinding is ensured by: (1) having blinded evaluators administer the assessments of aerobic fitness, cognition, and daily functioning; (2) minimizing the

exposure of research evaluators to participants and clinical staff at exercise sites; and (3) having aerobic fitness assessment technicians and cognitive and daily functioning evaluators located in separate areas from the exercise sites. Additionally, following randomization, participants are instructed not to disclose which training program they are completing to blinded research staff. Results from our earlier pilot study [74] indicate that the risk for un-blinding is minimal—only two of 41 subjects were un-blinded with no status disclosures during any of the cognitive assessments or clinical and functioning interviews.

ASSESSMENTS

The primary outcome measures of the trial are neurocognition and aerobic fitness, as indexed by the composite score of the MATRICS Consensus Cognitive Battery (MCCB) and VO_2max, respectively. Secondary outcome measures are daily functioning and serum-BDNF. Exploratory outcome measures include demographic and clinical covariates, biological measures relevant to weight and physical activity, and additional measures that may affect cognition or treatment response. All measures are collected for all participants at baseline (T_0), 6-weeks (T_1), and 12-weeks (T_2). All neurocognitive and daily functioning assessments are completed by qualified and trained raters, certified by the study PIs. Prior to rating patients, all raters were trained in administration and scoring of cognitive and clinical assessments whose scores were assessed for accuracy. A complete schedule of assessments is outlined in Table 2.

Primary Outcomes

Neurocognitive functioning

The composite score of the MATRICS Consensus Cognitive Battery (MCCB) [90] serves as the primary cognitive outcome measure. The MCCB assesses cognitive function in seven domains including speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. The MCCB is sensitive to change, including in response to AE-induced changes in aerobic fitness [74,91]. The MCCB has been used widely in SZ cognition trials, and allows for comparison to other intervention studies [92]. All tests are administered between 10:00 AM and 12:00 PM to minimize diurnal-related variability in cognitive performance [93].

Aerobic fitness

Maximal oxygen uptake (VO_2max) tests are completed under physician supervision using electro-magnetically braked cycle ergometers. Oxygen uptake and related parameters are measured at rest, during exercise, and during recovery. Heart rate (HR) is measured using a 12-lead electrocardiography (ECG) throughout all tests. Participant measurements include a 3- to 5-min resting baseline; a 3-min low resistance (10 Watts)

warm-up; a ramping exercise protocol of 10–50 Watts (set by ACSM predicted age, gender, and conditioning; maximal exercise norms reached in ~12 min); and an active recovery of approximately 3 min. During the VO_2max test, workload is increased 5–10 Watts every minute until one of the following criteria are satisfied: VO_2 plateau, 85% of maximal HR (220-age), a respiratory quotient ≥ 1.1, or reported exhaustion [94]. Pulmonary gas exchange and ventilatory variables are recorded breath-by-breath and averaged over 20 seconds. Prior research has demonstrated feasibility of VO_2max completion in SZ participants [74,77].

Secondary Outcomes

Daily functioning

The Specific Levels of Functioning (SLOF; informant version) [95] total score serves as the primary daily functioning outcome measure. The SLOF is a behavioral questionnaire administered to an informant who interacts regularly with the participant (typically a family member), and assesses current functioning across six domains: physical functioning, personal care skills, interpersonal relationships, activities of community living, work skills, and social acceptability. The NIMH-funded Validation of Everyday Real-World Outcomes (VALERO) study found the SLOF to be most related to performance-based indices of cognition and everyday living skills [96–98]. Secondary, complimentary measures of daily functioning include the UCSD Performance-Based Skills Assessment (UPSA) [99] and the Schizophrenia Cognition Rating Scale (SCoRS) [100]. The UPSA is a performance-based measure that has reliably demonstrated the ability to predict real-world functioning in schizophrenia [101]; it has high correlations with measures of personal care skills, interpersonal skills, and community activities [101,102], and has demonstrated high sensitivity to functional changes [103]. The SCoRS is a clinician-administered interview, to both participants and informants, which assesses cognition-related daily functioning. The SCoRS has been used as a co-primary endpoint measure in several phase-2 and phase-3 trials assessing cognition in schizophrenia, and has been permitted by the FDA for pivotal registration trials. It also has exceptional test-retest reliability, strong relation to cognition, and a high sensitivity to treatment [104–106].

BDNF

Serum BDNF is measured by ELISA method (R&D Systems, Minneapolis, MN). Intra- and inter-assay variability is 3.8% and 7.6%, respectively. Sensitivity is <20 pg/mL. The range in healthy people is 6, 186-42, 580 pg/mL. All samples are collected between 9:00 AM and 10:00 AM to reduce diurnal-related variability in BDNF [107,108]. Samples clot for 60 min at room temperature [107] and is removed after centrifugation at 3200 rpm at 4 °C, then frozen on dry ice and stored at −80 °C until end-of-study. Samples will be then be express shipped for analyses at the Human

Immune Monitoring Center (HIMC) at Icahn School of Medicine at Mount Sinai in New York.

Exploratory Outcomes

Clinical measures

Diagnoses is determined using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [108]. The SCID is used to confirm diagnosis of SZ or related disorders and the presence or absence of substance abuse or dependence. Current positive, negative, and general clinical symptoms are indexed using the Positive and Negative Syndrome Scale (PANSS) [109] and the Beck Depression Inventory (BDI-II) [110].

Measures relevant to weight and physical activity

Data on BMI, abdominal circumference, and blood pressure, as well as blood samples for fasting glucose and lipid panel (and thyroid-stimulating hormone (TSH) at baseline only) are collected at baseline, 6-weeks, and 12-weeks and will be assessed as possible mediators in future analyses. BMI is based on the participant's height and weight at baseline visit, and calculated using the following formula: (weight in pounds/(height in inches squared)) × 703. All blood samples are collected between 9:00 AM and 10:00 AM to minimize possible diurnal-related variability. These blood samples will be used as control variables as well as safety measures. Also, participants complete at baseline and 12-weeks physical activity self-reports (International Physical Activity Questionnaire; IPAQ) [111], in addition to using an accelerometer (Actigraph wGT3X-BT), to measure possible changes in "real-world" physical activity and sedentary behavior in order to explore links to aerobic fitness, metabolic health, and cognition. Accelerometry assessment is conducted over 7-day epochs using established cut points [112].

Other variables that may impact cognition or treatment response

Data on medications, menstrual phase, sleep, smoking, caffeine, metabolic indicators and other clinical and behavioral assessments are collected at baseline, 6-weeks, and 12-weeks. Demographic data are collected at baseline assessment. Antipsychotic medications are indexed by chlorpromazine equivalence. As other medications may affect outcomes, we track medication usage/change using three broad classes: (1) anti-depressants; (2) mood stabilizers; and (3) other medications. As scores allowing direct comparisons of medications are unavailable, for each class we document the use of relevant medications at baseline using a dummy variable, along with increases, no change, decreases, or discontinuation at follow-up assessments (1, 0, −1, or −2, respectively). We also inquire about use of medications that may influence cognition (e.g., antihistamines for allergies) during the 48 hours prior to cognitive and aerobic fitness tests.

We utilize a similar strategy to address medications known to affect biomarkers (e.g., SSRIs on BDNF).

We assess sleep (indexed using an adapted version of the Pittsburgh Sleep Quality Index; PSQI) [113] during the 24 h prior to cognitive testing. The PSQI has been used extensively in SZ studies [114,115]. If a participant reports substantial acute sleep loss that is likely to impact an outcome (*i.e.*, <4 h sleep) [116], assessments are postponed until sleep is restored. We assess smoking using the Fagerström Test for Nicotine Dependence (FTND) [117], along with the number of cigarettes smoked in the 4 hours prior to tests (nicotine half-life = ~2 h) [118,119]. The FTND has been used successfully in previous SZ studies [120].

Anxiety symptoms and alexithymia are measured using the Beck Anxiety Inventory (BAI) [121] and the Toronto Alexithymia Scale (TAS) [122], respectively. Emotion regulation strategies are measured using the Emotion Regulation Questionnaire (ERQ) [123]; emotion regulation, which has been observed to change in response to exercise [124], is also impaired among individuals with SZ and may predict functioning [125]. We assess subjective well-being using the Satisfaction with Life Scale (SWLS) [126], which has been used in prior SZ studies [127]. Childhood trauma is assessed using the Childhood Trauma Questionnaire (CTQ)[128]; this is especially critical, given the noted influence of trauma on BDNF [129]. Finally, we evaluate overall clinical symptomatology using the Clinical Global Impression scale (CGI) [130], while premorbid intellectual functioning will be determined using the Wechsler Test of Adult Reading (WTAR) [131].

Cognitive and clinical raters' proficiency

We conducted rater training in administration and scoring of cognitive, clinical, and functioning assessments (*i.e.*, MCCB, SCoRS, SCID and PANSS) prior to study initiation, along with subsequent re-training annually. All raters submit anonymized copies of the first 3 administered protocols (MCCB, UPSA, SCoRS, SLOF, and PANSS), followed by every 5th protocol, to ensure accurate procedures and check for completeness. Additionally, raters regularly discuss potential issues related to administration and scoring of measures with the study PI on an as-needed basis.

Participant reimbursement

The compensation for subjects who complete all research assessments is $260 for seven research visits and two week-long assessments with Actigraphs over 12 weeks ($50 for the baseline, $60 for the 6-week, and $150 for the 12-week assessment). Participants also receive $10 reimbursements for travel expenses for each research visit, as well as for each AE or ST training session they attend (paid weekly). As many individuals with SZ are dependent on limited disability benefits, the reimbursement for travel expenses was implemented to minimize the likelihood that participation in the study will be limited to individuals with

higher socioeconomic status or those living in close proximity to study sites.

Sample size calculations

The sample size for the protocol is 200 outpatient individuals with schizophrenia (SZ). We determined sample size based on our primary focus on the treatment effect of cognition, specifically the MCCB total composite score. Prior literature suggests that individuals with SZ score, on average, between 1 and 2.5 standard deviations below average on the MCCB [13,14,132,133]. Thus, we chose a clinically meaningful effect size of 0.50, or half a standard deviation in MCCB score, to be our target effect size for powering the trial. In our earlier pilot study [74], we found a large effect size for AE vs controls on cognitive functioning (Cohen's d = 0.93), suggesting improvement of 0.93 standard deviations among participants with SZ in AE training compared to controls. Assuming a loss-to-follow-up rate of 20%, with 80 participants (100 × 0.8) remaining in each arm, we are powered to detect moderate or larger effect size differences (*i.e.*, >0.45 Cohen's d) in cognitive changes in response to a 12-week exercise intervention, with >80% power. Therefore, the proposed sample size provides adequate power to detect a clinically meaningful effect size for our primary outcome.

Randomization and stratification

After completion of the baseline assessments, participants are randomly assigned to either an aerobic exercise (AE) or stretching and toning (ST) training. A total of 200 participants will be recruited across 4 sites and will be randomized in blocks of 4, 1:1 within each site to either AE or ST training. Study treatments are randomly assigned using a system developed by the study biostatistician, who generated a randomization scheme prior to the start of the trial, such that treatment assignment occurs probabilistically at the moment of randomization for each participant. Randomization occurs via the dedicated electronic management system created by the Statistical Analysis Center (SAC) at Columbia University Medical Center (CUMC). Once a participant's baseline assessment data is entered to the electronic database, the data management system generates an intervention group assignment.

Protocol deviations

The trial is designed using the intent-to-treat (ITT) principle, including all participants as randomized regardless of protocol violations. However, we will conduct separate modified "per-protocol" analyses, including only individuals who engaged in the interventions and have attended at least one exercise session. Such exclusion is consistent with strategies employed in previous intervention studies [134].

Statistical analysis and statistical tools

The primary aim of the study is to examine the efficacy of aerobic exercise to improve cognition in people with SZ. Specifically, we hypothesize that:

1. At 12-weeks, participants in the AE training will significantly improve their cognitive functioning compared to ST-controls.
2. Increases in aerobic fitness will predict improvements in cognition.

The secondary aims of the study are to examine the efficacy of aerobic exercise to improve functioning in people with SZ.

1. At 12-weeks, participants in the AE training will significantly improve their daily functioning compared to ST-controls.

The third aim of the study is to examine whether aerobic exercise-related changes in serum-BDNF mediate changes in cognition in individuals with SZ:

1. At 12-weeks, participants in the AE training will demonstrate significantly larger increases in serum-BDNF compared to ST-controls.
2. AE-induced improvements in cognitive functioning from baseline to 6 weeks to 12 weeks will be mediated by increases in serum-BDNF.
3. AE subjects with a robust early increase in serum-BDNF (measured at 6 weeks) will display enhanced 12-week cognitive improvements compared to those with a gradual response.

Additionally, we will explore the impact of potential biologically relevant covariates (e.g., sex, age, BMI), as well as intervention characteristics (e.g., fidelity with AE training intensity), on key outcome variables. Recent reports have linked cognitive functioning to inflammation markers [135,136], as well as other neurotrophins, both of which have been found to be susceptible to regulation by physical activity. Taking advantage of the present study's infrastructure, we will employ an analytic plan similar to the one used for BDNF and explore the links between changes in aerobic fitness, inflammation markers (TNF-α, IL-6, CRP), other neurotrophins (NGF, NT-3, NT-4), and improvements in cognitive functioning.

We will conduct all primary analyses on an ITT basis, such that all randomized participants will be analyzed according to the treatment they were assigned regardless of adherence to treatment. We will also perform statistical analyses controlling for fidelity level to training intensity, which will account for intervention adherence. Main statistical analyses will include variants of mixed effects regressions in order to model changes in cognition, functioning, and serum-BDNF levels as a function of time, treatment group, interaction of time-by-treatment group, and site. Additionally, we will use mixed effects regressions to assess changes in cognition predicted by contemporaneous change in aerobic fitness (indexed using VO_2max tests), controlling for treatment group and other

covariates. To assess potential mediation of serum-BDNF on the association between AE and cognition, we will fit a structural equation model with changes in serum-BDNF from baseline to 6-weeks as mediators of the relationship between AE intervention and early changes in cognition from baseline to 6-weeks, as well as later changes in cognition from 6- to 12-weeks. Additionally, we will use regression to estimate the association between continuous measures of training intensity and changes in cognition. We will also include sex, age, and baseline BMI as potential moderators of treatment effect by including interactions with treatment in analyses. We will analyze data using R, SAS version 9.4, and/or MPlus verison 8.3 [137].

Ethical considerations

The trial is approved by the Institutional Review Boards (IRBs) of Icahn School of Medicine at Mount Sinai (file number: 17-1511), University of North Carolina at Chapel Hill (file number: 17-2167), Augusta University (file number: 1123906-6), and Stanford University (file number: 43681). Trial registration has been completed at ClinicalTrials.gov (NCT03270098). At each site, the site PI will contact clinicians and inform them about the study, who will subsequently describe the study to potential participants and evaluate their interest. If the patient is interested and willing, a member of the research team will describe the study in more detail and invite them to enroll. As part of the informed consent process, the study rationale and methods will be described in detail and any questions will be answered. We will assure patients that participation is voluntary, they can withdraw at any time, and they will receive ordinary treatment whether or not they choose to participate. All prospective patients will be judged clinically competent to give written informed consent. We will obtain informed consent from all participants prior to study participation, using a consent form approved by the site's Institutional Review Board. We will administer assessments over multiple days, in order to avoid placing unnecessary strain on the individual. Also, the participant's targeted weekly HR will be based on the individual's baseline physical fitness level (*i.e.*, minimal and maximal HR), thereby ensuring that the intervention's targeted physical intensity level is safe to engage in. Participants who experience discomfort or chest pain while exercising will receive immediate examination by the study physician, and will ensure that the participant receives proper medical intervention, if necessary.

Adverse events

The principal investigator of each site is responsible for ensuring compliance with all procedures. A series of exclusion criteria will be methodically evaluated (e.g., medical examination, blood testing, medication adherence, clinical stability) prior to study inclusion. Patients' clinical status will be monitored, and participants who show severe psychological or symptomatic deterioration and/or if clinically necessary

for ethical or safety purposes will have their participation discontinued. In such cases, participants will be offered other treatment. Additionally, all participants will continue to receive their usual mental health treatment.

Emergency procedures

To minimize risk of medical emergencies, patients with untreated hypertension, cardiac disease, or other medical conditions that may interfere with study participation (e.g., malignancy, liver or renal impairment) will be excluded from the study. The study physician will perform a medical examination and review participant ECG and blood tests prior to study inclusion. During exercise sessions, if the participant reports chest pain, the session will be discontinued, and the study physician will be notified immediately. The physician will then evaluate the participant and make the determination for potential additional medical intervention. If chest pain resolves on its own but is suspicious for cardiac pain, then follow-up will be arranged with the participant's general medical physician; no further exercise sessions will be held for the patient until after this evaluation. If chest pain resulting from exercise does not resolve quickly, then emergency personnel will be notified and transfer to an emergency room ensured.

DISCUSSION

Converging lines of preclinical and clinical research support the premise that AE potentially improves cognition and subsequent functional outcomes in individuals diagnosed with SZ. Specifically, evidence from our previous pilot study [74], as well as other AE studies in SZ [63,64,69,138–145] suggest that AE training is an efficacious, non-stigmatizing intervention for improving cognitive functioning in individuals with SZ. However, the extant AE and cognition in SZ literature has a number of weaknesses, which the current trial aims to address. In the present study, 12-weeks of AE training is compared to a ST control intervention of similar duration, which has been previously demonstrated to improve cognition and functioning [74]. We aim to recruit 200 individuals diagnosed with SZ or related disorders, thereby establishing the first fully powered comprehensive study assessing the efficacy of AE to improve cognitive functioning in SZ. We will use well-validated measures of cognition known to assess multiple cognitive sub-domains, as well as VO_2max tests to assess aerobic fitness; these assessments will be administered at baseline (prior to training), midway into training (6-weeks), and immediately upon completion of training (12-weeks). Secondary outcome measures will include various measures of daily functioning (including self-report, informant, and clinician-based assessments), as well as serum-BDNF measurement to explore the potential mediating influence of BDNF on the relationship between AE and cognition in SZ. Regarding the exercise intervention, in addition to traditional exercise equipment, our study will

use active-play video games, which has proven successful in increasing aerobic fitness [85], specifically in this population [74]. Additionally, we will assess training fidelity not only through exercise training attendance, but also by tracking training intensity by utilizing HR monitors during each exercise session to quantify in-session intervention delivery. If we find that AE improves cognitive performance, aerobic fitness, and daily functioning compared to ST, it may have significant implications for future treatment of patients with SZ. If confirmed, the results of this trial may provide support for the development of novel behavioral treatments to treat cognitive deficits in individuals with SZ, as well as provide information about the mechanisms underlying cognition deficits in this population.

In the continued absence of medications that effectively improve cognition in patients with SZ, persistent cognitive deficits adversely affect the prognosis and functioning of many affected individuals. The present study will provide information about a novel AE strategy to improve cognition, and subsequent functional outcome, that can be widely implemented and thus have a significant public health impact. Information to be obtained on mechanism of action will have the potential to inform the development and improvement of future treatments of cognitive deficits in SZ.

Trial status

Recruitment began at the Mount Sinai site in April 2018, with recruitment at other sites initiating in May 2018. As of November 2019, a total of 64 participants were enrolled in the trial, with 45 participants randomized.

CONFLICTS OF INTEREST

The authors declares that they have no conflicts of interest associated with this project.

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