Aerobic Exercise for Cognition in Schizophrenia

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Study Protocol and Statistical Analysis Plan

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Schizophrenia (SCZ) is a severe, chronic, and disabling psychotic illness that affects approximately 87,000 Veterans. Although symptoms such as hallucinations and delusions can often be somewhat controlled by medication, negative symptoms (such as poor motivation and poor self-care) and cognitive impairments do not improve with currently available medications. Deficits in the performance of critical everyday functional skills, including social and occupational functioning, residential maintenance, medication management, and basic self-care are important and tragic consequences of SCZ. The majority of patients experience some form of impaired everyday functioning, whether in employment, independent living, or social functioning (Harvey et al. 2004). As a result, **rehabilitative treatment leading to disability reduction has the potential to benefit nearly every patient with SCZ**.

There is a large literature indicating that cognition in SCZ has the potential to be enhanced by behavioral interventions. Brain changes have been shown to accompany enhanced cognition with cognitive training SCZ, such as increases in plasma brain-derived neurotrophic factor (BDNF, a marker of brain plasticity) and normalization of sensory gating that is dependent on hippocampal circuitry. This hippocampal finding is particularly important because of the large literature demonstrating hippocampal abnormalities in SCZ and the link of hippocampal abnormalities to impaired cognition in SCZ. Participants with SCZ are capable of participating in aerobic exercise (AE) training and making gains in fitness. One small study reported improved short-term memory with AE compared to a control non-aerobic exercise, but few cognitive measures were done and the sample size was limited to 8 per group. Importantly, this study found increased hippocampal volume that correlated with gains in aerobic fitness and with cognitive improvement.

AE is known to confer many physical health benefits. The AE literature in animals and healthy aging populations is informative for this SCZ project. A number of recent studies indicate that AE is associated with cognitive gains in healthy aging subjects, and these gains correlate with hippocampal volume increases, that in turn correlate with increased BDNF and cardiovascular fitness. AE in rats increases BDNF mRNA, and this occurs prominently in the hippocampus. Taken together, these preclinical and clinical studies are consistent with the hypothesis that AE, via increases in fitness, induce BDNF increases that lead to brain changes, particularly (but not necessarily limited to) the hippocampus that subserve cognitive gains with AE. There are parallels between the reduced hippocampal volume in SCZ and the hippocampal volume loss seen with normal aging. It is possible that a similar mechanism may underlie potential cognitive gains with AE in SCZ.

AE is a potentially important means to improve cognition in SCZ, but work on cognitive effects of AE in SCZ is surprisingly sparse. **This project will fill this important knowledge gap.** The study will be a randomized rater blind parallel group clinical trial to compare twelve weeks of AE training with a control condition (CONT) consisting of stretching exercises in 40 participants aged 18-70 with SCZ or schizoaffective disorder. Specific Aims of the project are:

Specific Aim 1: Compare the feasibility and effectiveness of AE training to a CONT condition at the end of training (12 weeks) in VA participants with SCZ. We predict that completion of this training will be feasible in our VA population, and that the AE group will exhibit significantly greater cognitive improvement than the CONT group (measured by the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery, MCCB). The MCCB at *8 weeks post-training follow up will be a secondary outcome.*

Specific Aim 2: Evaluate whether increases in cardiovascular fitness mediate cognitive improvement. Cardiovascular fitness will be estimated with a reliable and valid measure of oxygen uptake (VO_2max) prior to and after 12 weeks of the AE vs. CONT intervention and at *8 weeks post-training follow up.* Estimated VO_2max is the most appropriate test as it accounts for initial fitness level of the participant without the physically exhausting and frightening experience of a full $V0_2$max test. We predict that estimated VO_2max improvement in the AE group will predict cognitive gain with training at 12 weeks and *8 weeks post-training follow up.*

Specific Aim 3: Compare changes in measures of everyday functional abilities (U. California San Diego Performance-Based Skills Assessment, UPSA) in the AE vs. CONT training groups. We predict that the AE group will show greater gains in the UPSA than CONTs at 12 weeks and *8 weeks post-training follow up.*

Improvements in cognitive function and skills of everyday living in SCZ are highly resistant to treatment with our current choices of medications. SCZ is generally a life-long condition: thus the disabilities with which these patients struggle will require treatment from the VA for the life of the patients. If AE leads to enhanced cognitive

functioning of these patients in everyday activities, AE could become a valuable treatment modality for the rehabilitation of SCZ patients, having dual benefits on both cognition and physical health. Hence this proposal is highly relevant to the VA mission of reducing impairments and rehabilitating our patients.

BACKGROUND AND SIGNIFICANCE

Functional and cognitive impairments in schizophrenia

SCZ is a chronic severe psychotic illness that affects over two million Americans. It ranks in the top ten causes of disability in developed nations (World Health Organization 1996). The annual cost of direct treatment has been estimated at $22.7 billion, while the overall costs of SCZ to our country are $62.7 billion (Wu et al. 2005). The annual cost of caring for these patients by the VA is nearly 2.5 billion dollars (Blow et al. 2011). 50-70% of those initially diagnosed with this illness have persistent symptoms throughout their lives (Harvey and Davidson 2002), frequently including impairments in employment, independent living, or social functioning (Harvey et al. 2004). Much of the cost of SCZ relates not only to treatment of acute symptoms, but to the chronic functional impairments that require intensive lifelong care (Wiersma et al. 2000; Wu et al. 2005). The severity of these functional impairments is strongly related to the severity of cognitive impairments. Medications for the illness are notably ineffective at reducing functional disability and cognitive impairments, thus explaining, in part, why antipsychotic medication alone is relatively ineffective at improving community functioning (Hegarty et al. 1994; Green 1996; Fenton and McGlashan 1994). As a result, effective **rehabilitation for disability reduction has the potential to benefit nearly every patient with SCZ**.

Cognitive enhancement and brain changes with cognitive training in SCZ

A large literature indicates that cognition in SCZ can be enhanced by behavioral training interventions (Wykes et al. 2011; Fisher et al. 2009; Fisher et al. 2010). A meta-analysis of cognitive training by McGurk et al. (2007) concluded that cognitive training can improve functional outcomes with a medium effect size, and is effective even for very chronic and highly impaired participants (Lindenmayer et al. 2008). Brain changes have been shown to accompany enhanced cognition with cognitive training SCZ. *Increases in plasma brain-derived neurotrophic factor (BDNF, a marker of brain plasticity) were seen in concert with cognitive gains after computerized training (Vinogradov et al. 2009a).* This same cognitive training system induced normalization in the P50 sensory gating paradigm that is *dependent on hippocampal circuitry* (Popov et al. 2011). *This hippocampal finding is particularly important because of the large literature demonstrating hippocampal abnormalities in SCZ, and the link of hippocampal abnormalities to cognitive dysfunction in SCZ (see reviews in Weinberger 1999; Pajonk et al. 2010; Boyer et al. 2007). For instance, people with SCZ have reduced hippocampal volume, disrupted hippocampal neuronal cytoarchitecture (Benes et al. 1991; Casanova and Rothberg 2002), reduced hippocampal NAA indicating reduced neuronal integrity (Weinberger 1999) and disrupted hippocampal glutamatergic (Tamminga et al. 2012) and nicotinic neurotransmission (Leonard et al. 1996).* The cognitive training studies cited above indicate that cognitive impairments in SCZ can be amenable to interventions, and participants are able to adhere to a program that lasts weeks to months. However, the literature on the effect of AE on cognition in SCZ is surprisingly sparse.

AE in SCZ: effects on cognition and brain function

Participants with SCZ are capable of participating in AE training and making gains in fitness (see review in Malchow et al. 2013). Participants in the studies reviewed in this paper maintained compliance with an AE program for six weeks up to 18 months, typically for three sessions per week. Most studies involved walking, jogging, or cycling as the AE. **Thus compliance with an AE program such as we propose herein is entirely feasible in a SCZ population.** Only one small study reported improved short-term memory with AE compared to a control non-aerobic exercise, but few cognitive measures were done and the sample size was limited to 8 per group (Pajonk 2010). **This project will fill this important knowledge gap.**

The dose of AE needed to produce optimal cognitive effects in a SCZ population is currently unknown. However the review by Malchow et al. (2013) demonstrates that the SCZ population is indeed capable of increasing cardiovascular fitness levels as measured by VO_2max in response to AE training parameters very similar or identical to the AE intervention we plan for this project (cycling, 3x per week, 12 weeks). Thus our choices of AE parameters are well supported by the literature and **provide support for our Specific Aims (SA)1-2**. Importantly, we have demonstrated that increases in estimated $V0_2$max does correlate with improved cognitive outcomes in healthy aging (Nocera et al. 2014; and see **Preliminary Studies** section below).

As noted,,the literature on brain changes with AE in SCZ is rather sparse. Pajonk et al. (2010) found increased hippocampal volume in SCZ after three months of AE (cycling) that correlated with aerobic fitness and with cognitive improvement; these changes were accompanied by increased hippocampal N-acetyl aspartate to creatinine ratio, a marker of neuronal integrity seen with magnetic resonance spectroscopy. In this same dataset Falkai et al. (2013) report increased cortical volume in their healthy controls, but their SCZ subjects did not have cortical volume increases. Taken together, these papers suggest that hippocampal changes but not cortical volume increases may in part mediate cognitive gains with AE in SCZ.

What can we learn from the aging and preclinical literature on AE that informs this SCZ project?

Advanced age, even in healthy populations, is accompanied by hippocampal volume loss and cognitive decline (Raz et al. 2005). Importantly, the cognitive decline commonly seen in older adults can be offset by greater levels of cardiovascular fitness (Colcombe et al. 2003). Several studies indicate that AE positively affects cognition in healthy older adults as well as many patient populations. For example, our work shows that AE improves language outcomes in previously sedentary older adults (Nocera et al. 2014) and Parkinson's disease (Nocera et al. 2010; Nocera et al. 2013).

A number of brain changes have been reported following AE as well. In animal models, AE increases new neurons in the hippocampus, increases neuronal spinal density, enhances neuroplasticity, and increases neurotropic factors (see reviews in Kramer and Erickson 2007; van Pragg 2008). Specifically, AE in rats increases BDNF mRNA, and this occurs prominently in the hippocampus (Neeper et al. 1995; Neeper et al. 1996). BDNF, in turn, promotes neurogenesis, synaptogenesis, and brain plasticity (see reviews in Cotman and Berchtold 2002). Importantly, select benefits of AE in the animal model have been translated to the human condition. For example, increased hippocampal volume is seen in older adults following AE. These hippocampal volume increases were highly correlated with (1) improved memory, (2) increased serum levels of BDNF, and (3) increases in VO_2max (Erickson et al. 2011). Taken together, these preclinical and clinical studies are consistent with the hypothesis that AE, via increases in VO_2max, induce BDNF increases that lead to brain changes, particularly (but not necessarily limited to) the hippocampus that subserve cognitive gains with AE (Cotman and Berchtold 2002).

Regarding **mechanisms of brain changes that could potentially mediate improved cognition in SCZ** with AE, much remains to be learned. There are parallels between the reduced hippocampal volume in SCZ and the hippocampal volume loss seen with normal aging. It is possible that a similar mechanism, involving enhanced VO_2max leading to increases in BDNF and downstream hippocampal changes could underlie cognitive improvements with AE in the elderly and in subjects with SCZ. This possibility is in accord with the finding of Pajonk et al. cited above (2010) of increased hippocampal volume in SCZ after AE correlating with fitness and cognitive improvement. The increases in BDNF in SCZ with cognitive training mentioned above (Vinogradov et al. 2009a) may be an illustration of an alternate method to achieve BDNF-induced brain changes. BDNF is a potential outcome measure for a larger study following this pilot study. Importantly for this project, an advantage of AE over cognitive training for cognition in SCZ is that AE stands to benefit the patients from a cardiovascular and medical standpoint as well as improving cognition.

PRELIMINARY STUDIES

The Duncan lab has extensive experience in the successful recruitment of SCZ participants at the VA for our prior work, including work on cognition and psychophysiology. Additionally, Dr. Nocera (Co-Investigator) has a successful track record of using effective exercise interventions to improve physical and cognitive outcomes in healthy older adults as well as patient populations. Below are highlights of our recent work.

1. Work in the Nocera Exercise Lab: AE to improve cognition in older adults supporting SA1 and SA2.

Table 1. Percent change in cognitive tasks pre to post in the exercise group (n=10) vs. control group (n=8)

Cognitive Task	Exercise	Control
Digit Ordering	8.33%	-1.93%
Digit Forward	11.21%	3.42%
Digit Backward	6.67%	1.24%
Stroop Color Words	9.52%	-3.25%
Letter Verbal Fluency	13.72%	5.76%
Trails A (% change in sec)	-17.11%	-4.36%
Trials B (% change in sec)	-36.73%	-20.89%

In a recently published VA-supported study, 18 previously sedentary older adults (aged 71.9±5.2) were randomly assigned to 12 weeks of 3 times weekly AE training (same as proposed in this application) or to a control group. Measures of frontally meditated cognitive executive function improved following AE. **Table 1** outlines the dependent measures of interest and percent change from pre to post intervention in both groups. More specific to the primary outcomes, there were no significant differences in baseline assessment

(verbal fluency or estimated VO_2max) between the AE group and the CONT group ($p > 0.05$). Additional analysis demonstrated that the AE group had a significantly higher estimated VO_2max ($p = 0.02$) and higher verbal fluency output ($p = 0.03$) when compared to the CONT group at posttest. A follow-up correlation analysis demonstrated a significant within group correlation between increases in estimated $V0_2$max and verbal fluency ($r = 0.54$; $p = 0.05$). Importantly, adherence (attendance) to the exercise was 82.5 percent (Nocera et al. 2014). Similarly, we have demonstrated improved functional outcomes and successful adherence and retention rates in other published exercise intervention studies (Nocera et al. 2013). **These data provide support for SA1-2.**

2. Study of cognitive training in SCZ in the Duncan lab

Dr. Duncan was the site PI for a multisite study funded by the NIH/Schizophrenia Trials Network and that compared computerized cognitive training to a computer games control in SCZ (1RC3MH090833-01, "eCaesar Study"). For this study we were very successful in retaining our participants (85% retention rate). The blind has not been broken so no pilot data are available, but our experience with this study demonstrates our ability to retain SCZ participants in prolonged interventional studies, **as for SA1**. For this study we are collecting the MCCB battery, **thus supporting our capability of performing this measure for SA1.**

3. Previous Duncan lab studies on SCZ collecting measures for Spec Aims 1 and 3.

Our previous CSR&D Merit funded project centered on the investigation of heritability of acoustic startle and cognitive measures in SCZ and healthy control probands and their families. Since the science of this large project does not have direct bearing on the current proposal, we have omitted details of our results (see Hasenkamp et al. 2010). We collected MCCB battery data for this study (Hasenkamp et al. 2011). We fully met our recruitment goals, enrolling 188 SCZ participants as well as a large group of control participants and their families. This provides evidence of the success of the Duncan lab in recruiting SCZ participants from the Atlanta VA and the surrounding community. Additionally we conducted an NIMH funded study of cognitive and real life function in SCZ (5 R01 MH078775-01) that involved collection of the MCCB battery and the UPSA. Thus **we have extensive experience with planned outcome measures for the current proposal**.

RESEARCH DESIGN AND METHODS

Study Design: The study will be a randomized parallel group clinical trial to compare twelve weeks of AE with a control condition (stretching and balance training) in 40 participants with SCZ (20 per group).

Description of study population: Participants for the study will be 40 participants treated at our Atlanta VA with a diagnosis of SCZ. Diagnosis will be confirmed by chart review and by a structured diagnostic interview (Structured Clinical Interview for DSM-IV, SCID-Axis I, patient version). Inclusion/exclusion criteria will be evaluated by means of chart review and participant interview.

Inclusion criteria: (1) Diagnosis of SCZ; (2) male or female, ages 18-70; (3) maintained on stable doses of outpatient psychiatric medications for at least 30 days; (4) compliant with outpatient follow-up (defined as coming for at least 75% of outpatient appointments within the previous 12 months); (5) have a stable place to live; (6) access to transportation to the VA. Participants will be sedentary as defined by reporting <20 min/week of performing regular physical activity in the past month.

Exclusion criteria: (1) Bipolar disorder;

- Criteria to rule out participants unlikely to be able to comply with treatment schedule: (2) active substance dependence within the prior 30 days; (3) more than 2 psychiatric admissions within the prior six months
- Criteria to rule out participants unlikely to be able to benefit from treatment: (4) known HIV infection or AIDS; (5) history of traumatic brain injury; (6) seizure disorder; (7) known Alzheimer's disease or other dementia; (8) clinical history of mild cognitive impairment (MCI); (9) Parkinson's disease; (10) other current clinically significant neurological disease, (11) unstable medical condition that would be expected to interfere with fitness training; (11) significant hearing or visual impairment.

Description of the intervention

For the **AE training**, participants will follow the guidelines authored by the American College of Sports Medicine (1998) for optimizing cardiovascular fitness. AE in accord with these guidelines have been used in prior studies of SCZ participants (see discussion of Malchow et al. (2013) review in **Background**. Thus, participants will exercise 3 times a week on a stationary bicycle ergometer consistent with Dr. Nocera's past and ongoing work on AE in aging and Parkinson's disease. Exercise intensity will begin at low levels (50% of maximal heart rate reserve) calculated utilizing the Karvonen method. Briefly, target exercise HR is calculated by subtracting the person's age from 220. Resting HR is then subtracted from this number. The answer is then

multiplied by the target percent (50% for example) and the product is added back to resting HR to provide the target exercise session HR (Karvonen et al. 1957). Intensity will be increased by 5% every week (as tolerated by the participant) to a maximum of 80% of maximal heart rate. Exercise time will progress from an initial 20 minutes per session to a maximum of 45 minutes by increasing 5 minutes each week. Each session will be monitored by the certified CPR and exercise physiologist/fitness specialist in Dr. Nocera's lab, Kevin Mammino. In addition, a research coordinator trained and highly experienced in working with SCZ (Bruce Cuthbert in the Duncan lab) will be present at all exercise sessions in order to enhance participant retention. To maximize safety, all participants will be cleared by a physician prior to beginning exercise training. Training will be conducted in the Nocera lab in the Atlanta VAMC, where portable defibrillators are readily available.

The **CONT condition** will consist of progressive whole body stretching and toning exercises delivered with the same contact hours as the AE. "Stretching" controls groups have been utilized in previous studies examining cognition vs. AE and have not resulted in improvements in cognitive function (Kramer et al. 1999). Study staff trained by Dr. Duncan will be present in all training sessions in addition to the exercise physiologist RA working with Dr. Nocera.

Primary and secondary outcome measures

(1) Primary outcome measures:

Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (**MCCB**). The National Institute of Mental Health funded the development of a consensus battery of neurocognitive tests for use in SCZ cognitive trials. The result is the MATRICS Consensus Cognitive Battery (MCCB). It assesses seven key cognitive domains relevant SCZ: processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. The MCCB has excellent test-retest reliability (Nuechterlein et al. 2008). It is the recommended outcome measure for SCZ cognition trials (Keefe et al. 2010). *The MCCB composite score at 12 weeks will be the primary outcome measure.*

(2) Secondary outcome measures:

a. To confirm the cardiovascular effects in the AE group we will perform an exercise test on all participants. Cardiovascular fitness will be estimated by the YMCA sub-maximal cycling protocol at Baseline, *Endpoint (12 weeks), and at 8 weeks post-training follow up.* Estimated **VO_2max** is the most appropriate test as it accounts for initial fitness level of the participant without the physically exhausting and frightening experience of a full $V0_2$max test. This is particularly critical since our population will be sedentary. This test uses an "extrapolation" method in which heart rate (HR) workload values are obtained at 4 points and extrapolated to predict workload at the estimated maximum HR (MHR) (e.g. 220 minus age in years). VO_2max is then calculated from the predicted maximum workload. Participants will be asked to ride a stationary bicycle for 4 three-minute stages. The first stage is a warm-up at 50 revolutions per minute (RPM) at a power level of 25 watts. During all testing stages, HR will be continuously monitored and will not exceed 85% of age-predicted maximum HR. Average HR during the final 30 seconds of the 2nd and 3rd minutes will be plotted against workload. Three-minute trial workloads will be chosen based on the participants' HR at the end of the warm-up period. The fourth 3-minute stage will be a cool down period at the end of the test. Participants will be allowed to stop the test at anytime if they feel faint, dizzy, short of breath, or for any other reason.

b. Ultimately, the goal of AE for cognitive remediation is to help our patients achieve improvements in real-world functioning and psychiatric stability. The U. California San Diego Performance-Based skills assessment (**UPSA**) is a measure of functional ability that can detect immediate improvements in the ability to carry out functionally meaningful tasks (Patterson et al. 2001; Harvey et al. 2007). It has excellent test-retest reliability (Leifker et al. 2010) and is able to quantify the potential for functional improvement with cognitive change (Green et al. 2011). As such, the UPSA is an excellent predictor of real-world functional outcomes (Mausbach et al. 2008; see Leifker et al. 2011 for a review). This literature supports our plan to use this measure in **SA3** at Baseline, *Endpoint (20 weeks), and 8 weeks post-training follow up.*

c. MCCB domain scores will be used as secondary outcome measures at Baseline, Endpoint (20 weeks), and 8 weeks post-training follow up, as will MCCB composite scores at 8 weeks post-training follow up.

Because it is crucial that staff expectations not bias our results, the research assistant (RA) doing the cognitive and symptom assessments (Molly Fargotstein) will be blind to the participant group assignment. Dr. Duncan will serve as a blinded back-up rater; she and Ms. Fargotstein already have established 90% inter-rater reliability. We have used this arrangement for our cognitive training study and have not had any instance of the blind being broken. The exercise training room is far removed from where we do cognitive assessments.

Additional measures to be collected

Current symptoms will be rated by means of the Positive and Negative Symptom Scale (PANSS; Kay et al. 1987) at Baseline, Days 28 and 56, Endpoint, and at 8 weeks post-training follow up. As per new FDA requirements governing management of suicidality in clinical trials, the Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered at these same time points. Anticholinergic load of current medications will be calculated as per methods of Vinogradov et al. (2009b) and used as a covariate in the analyses because this factor can affect cognitive gains in cognitive training studies.

Additional Fitness Measures for Specific Aim 2.

1. 400 Meter Walk. Participants will be asked to walk at their usual pace, without over-exerting. They can stop for up to 1 min for fatigue or other symptoms. A time limit of 15 minutes to perform the test has been established based on the following considerations. First, individuals who complete the walk in >15 minutes have an extremely slow pace (<0.44 m/sec), which would make their walking capacity of little utility in daily life. Second, selecting a higher cut-point, such as 30 or 60 minutes makes the objective assessment impractical and does not add to the clinical significance of the outcome. Participants will be allowed to use a cane, but not a walker, to complete the 400 m walk. Procedurally, we will first request that participants attempt the walk without the use of a cane. Those who feel unsafe will be allowed to attempt the walk with their cane.
2. Walking and Walking While Talking. Participants will be asked to walk across an electronic walk way which captures walking speed and foot placement in a quiet well-lit hallway wearing comfortable footwear. Start and stop points 10 meters apart will be marked by lines on the floor and include 3 feet from the walkway edge for initial acceleration and terminal deceleration. Seven walking trials will be randomly conducted; 3 single task walking only trials and 4 dual-task walking while talking trials. For the walking while talking trials participants will be asked to recite alternating letters of the alphabet. The order of the initial letter will randomly vary between “A” and “B” to minimize practice effects and/or count backwards by 3’s (Guralnik et al. 2000).
3. Short Physical Performance Battery (SPPB). The SPPB is based on a timed short distance walk, repeated chair stands and a balance test (as described by Guralnik et al.[17]). The battery will be administered by a trained and certified examiner.

Table 3.	***Screen/***	***Weeks***		***Weeks***		***Weeks***	***Endpoint***	***20 weeks***
Measure	***Baseline***	***1-4***	***Day 28***	***5-8***	***Day 56***	***9-12***	***Day 84***	***8 wk F/U***
Consent, HIPAA	X							
Psych, Medical Hx	X							
SCID	X							
Urine Toxicology	X						X	X
PANSS	X		X		X		X	X
C-SSRS, re suicide	X		X		X		X	X
Randomization	X							
AE vs. CONT: 3 sessions/wk		X		X		X		
MCCB	X						X	X
VO_2max	X						X	X
400 Meter Walk	X						X	X
Walking+Talking	X						X	X
SPPB	X						X	X
UPSA	X						X	X
SLOF	X						X	X

See Table 3 for **Timeline**. We will track the attendance of each participant, and will call to ascertain the reasons for missed sessions. Reasons will be compiled as pilot data for planning a larger study.

Statistical analysis plan

Specific Aim 1: Compare the feasibility and effectiveness of AE

training to a CONT condition at the end of treatment (12 weeks) in VA participants with SCZ or schizoaffective disorder. We predict that the completion of this training will be feasible in our VA population, and that the AE group will exhibit significantly greater improvement on the MCCB than the CONT group.
Statistical analysis: Basic statistical comparisons will be performed preliminarily before using a unified statistical approach. Two-sample t-tests using the change in cognitive tests and functional scales as dependent variables will compare AE to CONT participants. The statistical methodology includes both initial descriptive comparisons followed by a more complex unified statistical approach. Spec Aim 1 will ultimately be addressed in a full Merit project using a linear mixed model that is conceptually similar to analysis of variance (ANOVA). However, in this Pilot proposal we will build intuition about the model and the expected results by performing simple comparisons of direct interest prior to complex modeling. To accomplish this preliminary descriptive step and test our hypothesis we will use a univariate analysis of covariance (ANCOVA) looking at change scores with baseline measures plus age, sex, and anticholinergic load as covariates. We predict that greater anticholinergic load of medication will predict poorer improvement. With a sample size of 20 completers per treatment group, we will be sensitive to a within-between interaction effect size of f=0.456 at an alpha level of 0.05 with a power of 0.80. This can be interpreted as a sensitivity to between group difference in change scores of 9.5 MCCB composite t-score units (mean=50, SD=10), which is a meaningful clinical effect.

We will also undertake exploratory (non-inferential) analyses to estimate the strength of association of multiple dependent measures from the cognitive and functional domains. Data reduction via factor analysis will be performed for the MCCB battery data to reduce the number of dependent measures. Because the analysis of this data will employ multiple independent analyses, uncorrected significance tests will not be appropriate for inferential interpretation. However, uncorrected p-values will be reported as arbitrary criteria of effect size strength in deference to widespread use in social science for exploratory analyses.

To assess feasibility we will collect data on the numbers of SCZ participants who are potentially interested in participation, the number who screen out and for what reasons, the number of drop outs, and the reasons for their dropping out. We will also collect data on attendance and barriers to attendance. For these measures we will compute descriptive statistics. These data will inform proposals for fully powered future studies.
Specific Aim 2: Evaluate whether increases in cardiovascular fitness (VO_2max) mediates cognitive improvement. We predict that the degree of estimated VO_2max improvement in the AE group will predict the degree of cognitive improvement with training.
Statistical analysis: We will assess potential mediator effects of VO_2max as well as potential moderator effects of age, sex, and anticholinergic load to better formulate covariates in future models. The association between potential moderators and cognitive improvement will be evaluated through use of bivariate and multiple correlations; only significant associations will be further assessed as possible moderators. The assessment of VO_2max as a potential mediator will be evaluated using partial correlation coefficients from the regression model. With a total sample size of 20 participants in the treatment group, we will be sensitive to a bivariate effect size of r = 0.428 at an alpha level of 0.05 with a power of 0.80. This would allow us to detect differences of up to 18% in potential moderator variables. In a multiple regression with four predictor variables (because of issues of multicollinearity with anticipated high degrees of correlation possible between the potential moderator variables, it is doubtful that we will have a viable model with more than four predictors), we will be sensitive to an overall effect size of f2 = 0.063. Although sensitivity is provided, we consider the analyses used in the evaluation of this pilot data to be focused on estimation of effect sizes for future studies rather than for inferential interpretation. Because of this, p-values (and criterion alpha levels) will not be corrected for multiple independent testing. We will also run an exploratory regression model with mean training hours per week.
Specific Aim 3: Compare changes in performance-based measurement of functional abilities (by the UPSA) in the AE vs. CONT training groups. We predict that the AE group will have greater improvement in the UPSA than the CONT group at the end of treatment and at three months follow up.
Statistical analysis: The statistical approach for Spec Aim 3 will be similar to that of Spec Aim 1. Descriptive statistics will be generated with 95% confidence that our sample-based estimates will be within 0.20 SD of the population values. Hypotheses will be tested (and effect size estimates will be generated) with a univariate ANCOVA looking at change scores with baseline measures plus age, sex, and anticholinergic load as covariates. With a total sample size of 20 participants per group we will be sensitive to an effect size in UPSA scores of f=0.481 (alpha=0.05: power=0.80). This power and effect size will enable us to detect changes in UPSA scores of about 14%, a clinically meaningful change. A similar analysis (with identical sensitivity) will be used to assess the stability of the treatment effect through a univariate ANCOVA of change scores between the post-treatment and 3 month follow up measurements with post-treatment scores used as the covariate.

Sample size determination

Sample size calculations for our primary outcome measure (MCCB) are based on several studies of AE compared to a control condition in which the effect sizes average approximately 0.5 (Dustman et al. 1984; Fabre et al. 2002; Heyn et al 2004; Hotting et al. 2012; Chapman et al. 2013). We also based estimated power on studies of cognitive remediation in SCZ, including a meta-analysis (Wykes et al. 2011) and studies of Posit Science computerized remediation (Fisher et al. 2010). The average effect size of the above studies is 0.5. With alpha set at 0.05, an effect size of 0.5 will yield a power of 0.80 for our **planned sample size of 20 completers per treatment group** *(with dropouts replaced).* This sample size will be adequate to detect significant between group differences in MCCB change scores. More importantly for a pilot study, this sample size will allow us to estimate effect sizes specific to the target Veteran population with sufficient confidence to be useful in determining the sample size required for a future full Merit Review proposal (if indicated by the results of this pilot study). Participant retention will be an important issue. We estimate liberally from our prior work (cognitive remediation study) that *dropouts will be approximately 25%, so we will need to recruit 53 subjects in order to obtain the 40 completers needed for analysis.*

Roles of members of the research team. Please see delineation of roles in Budget Justification.

Description of relevance to VA

The deficits in function seen in so many of our VA SCZ patients are generally a life-long condition: thus the disabilities with which patients struggle require lifelong treatment from the VA. Improvements in cognition and everyday functioning are highly resistant to currently available treatments. Hence this proposal is highly relevant to the VA mission of rehabilitation and improving our patients' lives. Should our hypotheses be borne out in this study and in a full Merit study, our results will provide impetus to make AE part of the standard of care for SCZ, thereby leading to very real and crucially important gains for our patients.

Potential challenges to completing the work, and how we will address them

(a) *Recruitment and retention* is always a potential issue. Please see details about our methods for recruitment and excellent track record in **section 4, Human Subjects, subsection 2a, Recruitment**.

(b) *Retaining participants* throughout the intervention will be crucial. We do not have current funds to gather pilot data on AE in SCZ to provide retention statistics for the proposed design, but our retention in AE in non-psychiatric participants in Dr. Nocera's lab is 82.5%, and we have retained 83% of participants in our eCaesar study, a study that lasts twice as long. The literature on AE in SCZ demonstrates the feasibility of this approach. Mr. Cuthbert (the trainer for the eCaesar study) will be the chief staff member to supervise the training. Our participants form an excellent therapeutic alliance with Mr. Cuthbert, who has experience in retaining participants for up to a year in prior studies in our lab. See further comments on recruitment/retention in **section 4, Human Subjects, subsection 2a, Recruitment**.

(c) *Potential inability of SCZ participants to tolerate AE.* Dr. Nocera has an excellent record of retention in his AE studies. Poor adherence is also a potential challenge. Common causes of poor adherence include vacations, spouse care, fatigue, and fluctuations in motivation. For all study arms, we will use a social problem solving model approach in dealing with individual adherence problems. Our team has successfully applied this problem-solving approach to promoting continued adherence in a number of our previous studies.

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1. RISKS TO SUBJECTS

a. Human Subject Involvement and Characteristics:

Inclusion/exclusion criteria will be assessed for each participant by means of computerized chart review as well as participant interview and, were applicable, discussion with the participants' VA clinician.

i. Participants with SCZ. We will recruit 40 male and female participants with SCZ, aged 18-70. A diagnosis of SCZ, any subtype, will be confirmed by SCID. Inclusion criteria will be: (1) Diagnosis of SCZ; (2) male or female, ages 18-70; (3) maintained on stable doses of outpatient psychiatric medications for at least 30 days; (4) compliant with outpatient follow-up (defined as coming for at least 75% of outpatient appointments within the previous 12 months); (5) must have a stable place to live; (6) access to transportation to the VA. The participants will receive a psychiatric and medical history and be excluded if they have: (1) Bipolar disorder; (2) active substance dependence within the prior 30 days; (3) more than 2 psychiatry admissions within the prior six months, (4) known HIV infection or AIDS; (5) history of traumatic brain injury; (6) seizure disorder; (7) known Alzheimer's Disease or other dementia; (8) clinical history of mild cognitive impairment (MCI); (9) Parkinson's Disease; (10) unstable medical condition that would be expected to impair attention; (11) hearing impairment; (12) visual impairment (worse than corrected 20/40 by eye chart screening).

b. Sources of Research Material:

Research data will be collected solely for purposes of research unless otherwise specified. The research data obtained from human participants in this protocol will be as follows:

i. Clinical information obtained by medical history and psychiatric interview, symptom ratings, and cognitive testing.

ii. Clinical information obtained by chart review of the participants' clinical records to help in clarifying diagnostic and course information.

iii. Urine for toxicology. Urine samples from all participants will be tested for the presence of street drugs of abuse. This data will be collected solely for research purposes.

iv. Results of $V0_2$max assessment and performance during AE training. These data will be collected solely for research purposes.

v. Results of cognitive and functional performance testing. This will be done as part of the research protocol.

c. Potential Risks:

All risks described are research risks. No procedures done in this project will be done as part of the participants' clinical care.

i. *Risk of obtaining clinical information by interview, ratings, and chart review.* The risks here involve potential loss of confidentiality, and emotional upset if information gathered is of a highly emotionally charged nature.

ii. *Risk of obtaining clinical information by chart review.* The only risk regards potential loss of confidentiality.

iii. *Urine for toxicology.* The only risk regards potential loss of confidentiality.

iv. Risk of $V0_2$max assessment and performance during AE training. The risk is of fatigue and shortness of breath, increases in heart rate and blood pressure. There is a minimal risk of a cardiac event.

v. Risk associated with cognitive and functional performance testing. The only risks are of mild frustration.

2. ADEQUACY OF PROTECTION FROM RISK

a. Recruitment and Informed Consent:

i. Recruitment: Schizophrenia participants will be recruited from the clinical population of the Atlanta Veterans Affairs Medical Center. Clinical psychiatric facilities at the Atlanta VA Medical Center include a 40-bed admitting ward. There are approximately 1500 admissions per year, with roughly 30% diagnosed as having SCZ. Dr. Duncan is an attending on this ward, and is therefore personally familiar with the admissions to the inpatient service. Because the clinical population at the Atlanta VA is very large, there will be ample participants to recruit for this project. In fact, the total number of unique Veteran patients treated in our outpatient Mental Health clinics increased 10% in the past year and totaled 18,937 in 2011 (Northeast Program Evaluation Center data). Approximately 30% of these outpatients have SCZ (i.e. approximately 5700). Dr. Duncan works within a clinical team integrating inpatient and outpatient mental health staff and hence has ready access to recruit schizophrenia patients in the outpatient service. Additionally, the psychiatry

department at the Emory University is very active in research and has an extensive research infrastructure to aid in the recruitment of research participants.

In order to conduct recruitment for studies in the Duncan lab, we have set up the following specific procedures. With Emory IRB and VA R&D Committee approval, we have obtained a list of all patients with schizophrenia in the Atlanta VA. On a monthly basis we are able to pull all appointments in the Mental Health Clinic. For instance, in a recent month Dr. Duncan pulled appointments in our clinics for 670 unique VA patients with SCZ. Using a set of relational databases we are able to ascertain which of these patients with upcoming appointments have been diagnosed with SCZ. We give to each clinician a list of their patients with SCZ who are scheduled to come in that week (targeting a subset of clinicians each week). The clinicians then mention the study to appropriate patients during the appointment. If the patient is willing to speak with our research team directly, the clinician calls our lab to come down and meet with the patient after their appointment and, if they are willing, schedule a screening appointment with study staff. The intervention will be demanding of the participants' time and hence **retention will be an important issue**. Retention will be enhanced by modest participant payments to cover their travel expense ($30 per week). Transportation issues have the potential to limit participant participation. When possible, they will be helped to access transportation by the VA or the Disabled American Veterans (DAV) van system if needed. Additionally, we are able to provide a letter stating that our participants are receiving treatment for a serious mental illness. They can bring this letter to an Atlanta subway station and receive half-price passes to ride Atlanta trains and buses. Additionally, our VA is offering a growing network of shuttle buses that are free. **These transportation options have helped our participants remain on schedule for their training sessions in the eCaesar trial and we anticipate that these same options will help recruit and retain participants for this proposed study.**

ii. Consent procedures: This study will not be initiated until the protocol and consent form have been fully approved by the appropriate institutional review boards of Emory University School of Medicine and the Atlanta VAMC. Only participants who have given their written informed consent will take part in this study. Written informed consent will be obtained by Dr. Duncan or the research staff. Participants who have been declared incompetent will be included only if they have volunteered for the study, they have signed assent, and their conservator/guardian has signed informed consent.

All volunteers will be asked to sign consent after reading the VA consent form (10-1086), discussing the study, and being given a chance to ask questions. They will be informed that they are being asked to participate in a research study. Prior to signing informed consent, the participants will have the following elements of the consent form explained to them: the fact that participation is wholly voluntary, purpose of the study, procedures involved in the study, potential risks of the study, measures taken to minimize risks, potential benefits of the study, participant reimbursement for time and travel to participate, whom they can call (and phone numbers) if they feel they have been injured by participation or if they feel their rights have been infringed. They will be asked to read the consent form, and encouraged to ask questions or discuss any pertinent issues. They will be told that declining to serve as a participant in this study will not influence or compromise the quality of their care at the Atlanta VAMC (if they are Veterans and eligible for treatment at the VA). After participants have signed VA form 10-1086, a copy of their signed consent will be made and given to them. In accord with requirements at our VA, a copy of the consent form will be scanned into the participants' electronic clinical chart, and a note documenting the consent procedure will be entered into the electronic clinical chart. Participants will also be asked to sign a HIPAA consent, and the terms of this document will be explained to them prior to signing.

b. Protection Against Risk:

i. Risk of loss of confidentiality: All information will be stored in locked files in a locked research area that can be accessed only by members of the research team. Computer files containing research information will be kept on the private research local area network (LAN) belonging to the PI. This LAN is not accessible to others outside the Duncan lab. Files containing identifying information are password protected, and the computers are housed in the PI's lab. Only Dr. Duncan's research staff has keys that access this research area. No names or other identifying information will be used in publications that stem from this research. Under no circumstances will personally identifying information be released to any outside party (beyond those immediately connected with the study) without the written consent of the participant (or his/her guardian). There has been no breach of subject confidentiality from Dr. Duncan's lab in her 25 years of clinical research, so this risk is considered minimal.

ii. Risk of emotional upset during interviewing: The research assistants for the study, Mr. Cuthbert and Ms. Fargotstein, are both highly experienced in conducting interviews and research interactions with participants with SCZ. If a participant becomes upset at the clinical material being discussed, Dr. Duncan, an extremely experienced psychiatrist, will be available to intervene clinically. Additionally, the study will be conducted in the same building in which the participants' VA clinicians practice, so that a multiplicity of clinicians will be ready at hand if a participant becomes unduly upset.

iii. Risks associated with estimated $V0_2$max assessment and exercise training. Heart rate and blood pressure will change as a result of the VO_2 assessment and during the exercise sessions. Because of these changes there is a minimal risk of cardiac event. Although any exercise program carries the possibility of a cardiac event, we minimized this risk by requiring each participant to be cleared by a doctor. Importantly, exercise intensity will start out at low levels and increase as the participants tolerate. Participants will also be permitted to take breaks as needed if they experience discomfort, undue fatigue or shortness of breath, or any chest pain.

Participants will not undergo exercise stress testing. We considered adding an exercise stress test prior to randomization. An advantage of this would be that it would provide an additional opportunity to detect severe cardiac disease that might increase the risk of an acute event during our AE intervention. After extensive deliberations, our research team decided with unanimous vote that including an exercise stress was not necessary and would not add additional information for the study or protection to the human participants. This decision was based on the following considerations:

- The recommendations published in JAMA by Gill et al. (2000) advised that a screening protocol based on a simple cardiovascular reserve test, similar to the one we plan as described above is more suitable for screening adults than a protocol based on stress exercise testing.
- The American Heart Association (AHA) and the American College of Sports Medicine (ACSM) joint position statement advised that “apparently healthy persons of all ages and asymptomatic persons at increased risk may participate in moderate-intensity exercise without first undergoing a medical examination or a medically supervised, symptom-limited exercise test” (American College of Sports Medicine 1998).
- Participants with potential cardiac contraindications to the proposed exercise program will be identified and excluded by means of the screening process.
- Exercise of will be conducted in a supervised environment as described below in interventions section.
- We have found that a maximal or near maximal exercise test on a treadmill is an unpleasant, if not frightening experience, for sedentary and unfit adults.
- Regular exercise and physical activity may actually reduce the overall risk of myocardial infarction and death among older persons, possibly through improvements in cardiac risk factors and overall fitness (American College of Sports Medicine 1998).

In summary, we concluded that exercise stress testing would provide little additional information, was not necessary to protect the safety of participants, and that it is disliked by sedentary and unfit participants. Our protocol for the AE intervention also requires that the sessions carefully monitored for cardiac and other signs and symptoms by trained staff. To date, we have enrolled nearly 100 older adults, with and without neurological disease, in various exercise interventions and have no adverse events related to cardiac symptomology.

iv. Risks associated with cognitive and functional performance testing: The risks are minimal. If participants become frustrated, they will be permitted to take breaks from the assessments.

3. POTENTIAL BENEFIT OF THE PROPOSED RESEARCH TO THE PARTICIPANT AND OTHERS

The risks of this study are minimal since the procedures are noninvasive and protections are in place to minimize risks (see above sections on risks). All participants will receive monetary compensation for their time and travel incurred as part of their participation. The study may lead to knowledge that AE is effective in enhancing outcomes in VA patients with SCZ. The VA system could ultimately be spared the burden of protracted and incomplete rehabilitation of many of our patients with SCZ. The patients themselves will be afforded a greater chance to lead more functional and satisfying lives. Hence this proposal is highly relevant to the VA mission of rehabilitation of our Veteran patients.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Schizophrenia affects two to three million Americans, many of whom are Veterans. Schizophrenia is a very disabling disease with poorly understood etiology and pathophysiology. Persons suffering from this

disorder occupy one half of psychiatric beds in the U.S. and account for fully one third of VA inpatient days of care. Estimates of the cost of this illness have ranged from $20 billion to $48 billion annually. Our treatment of many of these Veterans with SCZ is protracted and of very limited success because many patients' symptoms are inadequately responsive to neuroleptics. The fact that currently available treatments leave many individuals with long-term disabilities and are ineffective in 20-30% of patients makes the advancement of our treatment of this disorder of urgent concern. Improvements in cognitive function and skills of everyday living are highly resistant to treatment with our currently available medications. The deficits in function seen in so many of our patients with schizophrenia create untold suffering for them and their families. Our study may lead to the adoption of computerized cognitive remediation as a way of enhancing outcomes in SCZ without incurring pharmacological risk.

5. DATA AND SAFETY MONITORING

The study will be overseen by the Data and Safety Monitoring Board (DSMB) at Emory University in the Department of Psychiatry and Behavioral Sciences. A report will be submitted to that DSMB on an annual basis, and the results of DSMB review will be reviewed in turn by Dr. Duncan and the study staff and filed with our IRB. Any safety problems will be addressed in consultation with our DSMB. Regarding data safety and integrity, the PI and study staff work closely with the R&D Service Line and the Research Integrity Officer and follow all recommendations to ensure data integrity. We take compliance extremely seriously, and all study staff participate fully in human subjects and research training both at the Atlanta VA and Emory University. We store hard copy study documents in locked file cabinets in a locked research area (Duncan lab) to which only our research staff have keys. Computerized data are stored in a set of relational databases customized by Dr. Duncan in Filemaker Pro. Dr. Delaune will work collaboratively with Dr. Duncan to customize databases for the specific data needs of this study. These databases are password protected, as are the computers our research staff use for access. The databases have data integrity checks built in. Only Duncan lab research staff have keyed access to the Duncan lab that houses these computers. The data is stored on a VA research drive that is managed by the IT service in concert with the R&D Service Line at the Atlanta VA. Our computer back-up procedures are thorough and include daily off-site back up as provided by an off-site VA server under management of the R&D Service Line.

5. VERTEBRATE ANIMALS - not applicable

Inclusion of Women and Minorities

Women have been included among our SCZ participants at approximately 10-15 percent. We will continue to strive to recruit female participants at a comparable rate. Minorities have been included among our participants at approximately 50 percent in the Duncan lab SCZ projects to date. We will continue to strive to recruit minority participants at a comparable rate.

Inclusion of Children

Children under the age of 18 may not be enrolled according to VA rules. Participants ages 18-21 will be included in numbers proportionate to their prevalence in the VA SCZ population. This proportion is steadily increasing as a result of the two current wars and the increase in young military recruits over the past few years.

Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: Cognitive Remediation Treatment for Severe Mental Illness

Total Planned Enrollment: 40

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	0	1	1
Not Hispanic or Latino	5	34	39
Ethnic Category: Total of All Subjects *	5	35	40
Racial Categories			
American Indian/Alaska Native	0	1	1
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	18	21
White	2	15	17
Racial Categories: Total of All Subjects *	5	35	40

*** The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."**