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A randomized controlled trial of exercise on augmenting the effects of cognitive remediation in persons with severe mental illness

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ABSTRACT

Background: Preliminary evidence suggests that aerobic exercise may augment the effects of cognitive remediation on improving cognitive functioning in severe mental illness. It has also been hypothesized that increases in cognitive functioning associated with adding exercise are mediated by increases in brain derived neurotrophic factor (BDNF). However, rigorous controlled trials are lacking.

Methods: A randomized controlled trial was conducted to explore whether adding a 30-h aerobic exercise program over 10 weeks to an equally intensive cognitive remediation program (CR + E) improved cognitive functioning more than cognitive remediation alone (CR-Only). Thirty-four participants with schizophrenia or bipolar disorder were randomly assigned to CR + E or CR-Only, and cognitive functioning was assessed at baseline and post-treatment. Total and mature BDNF were measured in blood serum at baseline, Week-5 pre- and post-exercise, and Week-10 pre- and post-exercise.

Results: Participants in both conditions had high levels of engagement in the interventions and improved significantly in cognitive functioning, but did not differ in amount of cognitive change. The groups also did not differ in changes in BDNF from pre-to post-exercise at Weeks 5 or 10, nor in resting BDNF levels. Exploratory analyses indicated that higher body mass index (BMI) significantly predicted attenuated improvement in cognitive functioning for both groups.

Discussion: Exercise did not augment the effects of cognitive remediation in persons with severe mental illness, possibly because the cognitive remediation program resulted in strong gains in cognitive functioning. Moderate aerobic exercise does not appear to reliably increase BDNF levels in persons with severe mental illness.

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Increasing research has focused on cognitive remediation to address reduced cognitive functioning in schizophrenia and other severe mental illnesses. Meta-analyses indicate moderate effects of cognitive remediation on improving cognition (McGurk et al., 2007; Wykes et al., 2011), but continued impairment after treatment is common, calling for more potent interventions. Physical exercise has been hypothesized to

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augment the impact of cognitive remediation (Campos et al., 2017).

The general health benefits of physical activity are well established, including the impact of exercise on cognitive functioning. Aerobic exercise increases blood flow to the brain and neurotransmitter levels, and has been shown to improve cognition across the human lifespan (Christie et al., 2017; Jonasson et al., 2017; Smith et al., 2010), as well as in clinical populations such as children with attention-deficit hyperactivity disorder (Ng et al., 2017) and adults with cardiovascular disease (Brunt et al., 2019), Parkinson's disease (Ahlskog, 2011; Nadeau et al., 2017), and dementia (Forbes et al., 2013). Preliminary evidence also suggests that exercise may improve cognition in severe mental illness (Firth et al., 2017; Kim et al., 2014; Kimhy et al., 2015; Shimada et al., 2019; Su et al., 2016). However, only two studies have examined whether exercise increases the impact of cognitive remediation in this population.

First, one randomized controlled trial (RCT) (Oertel-Knöchel et al., 2014) evaluated the effects of adding either 125 min/week of physical exercise or relaxation training to 90 min/week of cognitive remediation over four weeks in patients with severe mental illness. Participants in the exercise group improved more in working memory, but not processing speed or visual learning, than those in the relaxation group. A limitation of this study was that much less cognitive remediation was provided (i.e., 6 h over one month) than most other programs shown to improve cognitive functioning (i.e., average 20 h over several months) (Wykes et al., 2011), suggesting suboptimal dosing of cognitive remediation.

Second, a small non-RCT of 16 participants with recent-onset schizophrenia evaluated the effects of adding 150 min/week of exercise to four hours/week of cognitive remediation over ten weeks (Nuechterlein et al., 2016). Participants who received additional exercise improved more in cognition than those who received only cognitive remediation. Aside from the non-RCT design, a limitation of this study was that participants in the cognitive remediation only condition did not improve in cognitive functioning, suggesting that there were no remediation effects for exercise to augment.

This study was aimed at overcoming the limitations of previous research by rigorously evaluating whether aerobic exercise enhances the impact of an empirically supported cognitive remediation program on cognition in persons with severe mental illness (Lindenmayer et al., 2008; McGurk et al., 2005, 2015). A related question is the mechanism underlying the possible augmentation effects of exercise on cognitive remediation. Brain derived neurotropic factor (BDNF) is a neurotrophin involved in synaptic transmission and growth (Figurov et al., 1996; Korte et al., 1995) that has been proposed as a biomarker for cognitive enhancement (Bathjina and Das, 2015). Evidence of altered serum BDNF levels in schizophrenia suggests an important role of BDNF in the pathophysiology of schizophrenia (Green et al., 2011; Pandya et al., 2012). Exercise increases the levels of BDNF in the general population (Szuhany et al., 2014), with some evidence in schizophrenia (Kim et al., 2014; Kimhy et al., 2015), suggesting that increases in BDNF following exercise may mediate improved cognitive functioning. Two controlled studies of exercise interventions, one in older adults (Leckie et al., 2014) and another in schizophrenia (Kimhy et al., 2015), have reported such mediation effects for BDNF on gains in cognitive performance. This is the first study to evaluate whether increases in BDNF mediate cognitive gains of augmenting cognitive remediation with exercise in severe mental illness.

1. Methods and materials

An RCT was conducted comparing the effects of adding exercise to cognitive remediation (CR + E) to cognitive remediation alone (CR-Only) over 10 weeks, with changes in cognition from baseline to one-week post-treatment as the primary outcome. BDNF assessments were conducted at baseline and pre-post exercise (CR + E), and pre-post 1 h of rest (CR-Only) at 5-weeks and 10-weeks to evaluate whether exercise-related improvements in cognitive functioning were mediated by changes in BDNF level. All study procedures were approved by the Boston University (#3636) and the Massachusetts Department of Mental Health (#2016–08) Institutional Review Boards. The data from the study are available from the authors upon request.

1.1. Study site

The study was conducted at the Center for Psychiatric Rehabilitation at Boston University. The exercise program took place at the Boston University Fitness Recreational Center located across the street. Blood draws for the BDNF assays were conducted at physician offices located adjacent to the Center.

1.2. Participants

Inclusion criteria were: 1) DSM-5 diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder, or bipolar I disorder, based on the Structured Diagnostic Interview for DSM-5 (First et al., 2015); 2) stable prescribed psychotropic medication dosage or type for ≥1 month; 3) medical clearance from a physician to participate in the exercise program; 4) currently exhibiting a sedentary lifestyle (exercising <3 days/week for ≤20 min each time) (Dunn et al., 2005); 5) no active suicidal ideation; 6) cognitive impairment (mean < 1 SD below normal on the Trails B (Radford et al., 1978) or Hopkins Verbal Learning Task (Brandt, 1991);); and 7) fluent in English.

Exclusion criteria were: 1) positive screen for a major neurocognitive disorder (score <23 on Folstein Mini Mental Exam (Folstein et al., 1975) or a positive score on the HELPS Brain Injury Screening Tool with ≥2 chronic cognitive difficulties for Problems "P" component (Picard et al., 1991); 2) DSM-5 diagnosis of substance use disorder other than nicotine or caffeine in last 6 months, or bulimia in last 6 months; 3) body mass index (BMI) ≥40; 4) resting blood pressure ≥160 mg systolic and/or 100 mg diastolic; and 5) for women, currently pregnant, plans to be pregnant in the next year, or currently breastfeeding.

Thirty-four participants met inclusion/exclusion criteria, signed informed consent, completed the baseline assessments, and were randomized to either CR-Only ($n = 17$) or CR + E ($n = 17$). Fig. 1 provides the CONSORT diagram.

1.3. Assessments

The baseline assessment included a background interview, diagnostic assessment (SCID), psychiatric rating scales, a neurocognitive battery, and blood draws for BDNF assays. Psychotropic medications were coded for anticholinergic load based on Risacher et al.'s (2016) method for calculating Anticholinergic Burden Scores (ABS).

1.3.1. Cognitive and psychiatric functioning

Neurocognitive and clinical assessments were conducted at baseline and post-treatment by interviewers blind to treatment assignment. Premorbid functioning was assessed at baseline only with the *Wide Range Achievement Test* (Wilkinson and Robertson, 2006).

Cognitive functioning was evaluated with the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008), which includes: 1) Attention/vigilance: the *Continuous Performance Test-Identical Pairs Version*; 2) Verbal working memory: the *Letter-Number Span*; 3) Verbal learning: the *Hopkins Verbal Learning Test-Revised (HVLT)*; 4) Visual learning: the *Brief Visuospatial Memory Test (BVMT)* 5) Information processing speed: the *Trail Making Test A, Verbal Fluency, and BACS Symbol Coding*; 6) Planning/executive functions: the *NAB Mazes*. The Spatial Span and the MSCEIT were not administered; delayed recall trials for the HVLT and BVMT were added to assess memory, and the *Trail Making Test B* (Radford et al., 1978) was administered to supplement measurement of executive functions.

General psychiatric symptoms were assessed with the *Expanded Brief*

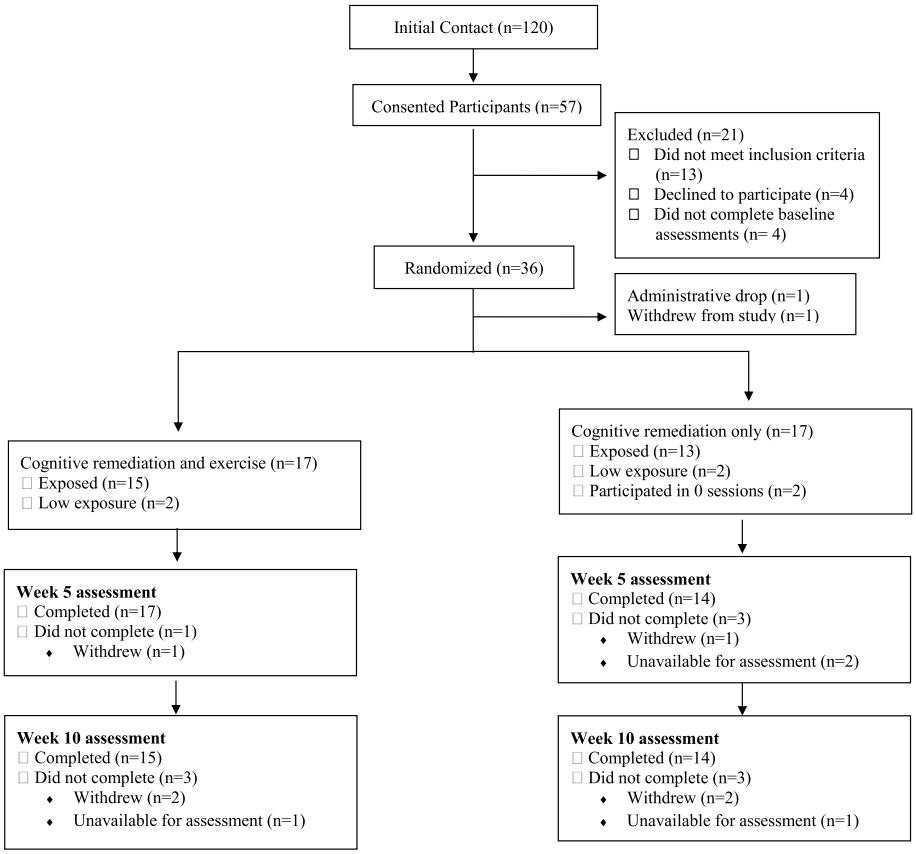


Fig. 1. CONSORT diagram.

Psychiatric Rating Scale (Lukoff et al., 1986). Depression severity was evaluated with the *Montgomery-Asberg Depression Rating Scale* (MADRS) (Montgomery and Asberg, 1979).

1.3.2. Physical activity

Physical activity over the past week was measured at baseline and post-treatment with the Short Form of the International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003), which converts activity into estimated metabolic equivalent expenditure (MET). Activity for all participants were also tracked throughout the study with *Fitbit Zip Wireless Activity Trackers*, which record the number of daily steps taken. Since we did not want to encourage participants in either group to exercise more than usual outside of the study sessions, the number of daily steps taken on the Trackers was masked. Participants' Fitbit steps were downloaded by synching the device weekly to a research computer. Based on review of the distribution of daily steps, days with <500 steps were excluded from the analyses.

For participants in CR + E, heart rate was measured before and during the workout part of the exercise classes with a fingertip heart rate monitor in order to regulate the intensity of the exercise to the desired 60–75% maximum heart rate range.

1.4. BDNF assay

Serum total and Mature BDNF were assayed with two different ELISA kits. Aviscera-Bioscience BDNF ELISA Kit assessed Mature BDNF and Quantikine Total BDNF Immunoassay assessed Total BDNF. Of note, Total BDNF includes activity of both proBDNF and Mature BDNF which have opposing effects on receptors involved in neuroplasticity and long-term potentiation, with proBDNF being an inhibitor of such processes (Hashimoto 2016; Yoshida et al., 2012). Thus, both types of BDNF measures are of interest here. Approximately 1 teaspoon of blood was drawn for assay at each of the 5 blood draws (baseline, pre/post exercise at Week-5, pre/post exercise at Week-10). Following time for blood to clot, samples were centrifuged and then stored at −80 C before batch processing. All blood draws were conducted in the morning, approximately between the hours of 9:30–11:30 a.m.

1.5. Interventions

All participants received cognitive remediation. Only participants randomized to CR + E received exercise. Both programs were conducted in small groups with open enrollment and rolling admissions for new participants.

1.5.1. Cognitive remediation

Participants received up to 30 h of computer-based cognitive exercises (1-h sessions, 3 times/week) with a widely used software package (Cogpack, Version 8.0, Marker Software) shown to improve cognitive functioning in prior studies (Lindenmayer et al., 2008; Lystad et al., 2017; McGurk et al., 2005, 2009, 2015, 2016; Sartory et al., 2005; Sato et al., 2014). Cognitive practice followed a standardized curriculum of exercises drawn from Cogpack, based on prior research on the Thinking Skills for Work program (Lindenmayer et al., 2008; McGurk et al., 2005, 2009, 2015, 2016), and tapped the broad range of cognitive functions. Cognitive remediation was facilitated by one or two cognitive specialists who provided strategy coaching to improve participants' performance on the exercises (e.g., chunking new information to optimize retention). Also based on prior research on Thinking Skills for Work (see above), completion of six of more cognitive training sessions was defined as sufficient "exposure" to the intervention to expect a cognitive benefit.

1.5.2. Exercise program

The exercise intervention was an equally intensive program (50-min

sessions, 3 days/week for 10 weeks) led by a mental health peer who was a certified fitness trainer, and usually co-led by a trained student. The program involved 40 min of aerobic exercise targeting 60–75% of maximum heart rate, with an additional 5-min warm-up and cool-down stretch. Following an introduction to the exercise training, participants chose an aerobic activity (e.g., stationary bicycle, walking/running track) to complete their exercise in any given session. The leaders helped participants initiate and maintain their program of exercise. The dose of moderate-intensity exercise was selected in order to match that shown to affect hippocampal volume and BDNF activity in sedentary aged adults (Erickson et al., 2012), and to target a level of exercise *below* that where negative effects are commonly experienced during exercise (Ekkekakis et al., 2011). After a progressive increase of aerobic intensity over the first 4 weeks, participants exercised at the study dose for the remaining 6 weeks of the study. As there was no a priori definition of exposure to the exercise intervention, "exposure" was defined using the same criterion as cognitive remediation: completion of six of more exercise sessions.

1.6. Procedures

Participants were recruited through pamphlets and advertisements posted in agencies serving people with severe mental illness throughout the Boston area, and referrals made following presentations about the project to staff at local agencies.

Following phone screening, participants were scheduled for a session to obtain informed consent, followed by administration of the two cognitive screening tests (Trails B and HVLT) and SCID to confirm cognitive and diagnostic eligibility for the study. Eligible participants then provided consent for physician contact for medical clearance, had their blood pressure checked and BMI measured, and completed the rest of the baseline interview. When physician clearance had been obtained, an appointment was made for the participant to have the blood draws, followed by randomization to CR-Only or CR + E by a computer program, stratified by diagnosis (schizophrenia-spectrum or bipolar disorder). To prevent significant imbalance between the two groups, randomization was constrained within each diagnosis strata to yield an equal number of participants assigned to each group every four sequential cases (two participants per group).

After participants were informed about their treatment assignment they were scheduled for their first intervention session(s). For the CR + E group, exercise classes were held in the morning three times per week, followed by a healthy light lunch provided by the study, and then the cognitive remediation session in the afternoon. Participants in the CR-Only group came in on the same days for lunch and completed the cognitive remediation session in the afternoon.

For the Week-5 and Week-10 BDNF assays, participants in CR + E came in for blood draws in the morning prior to their exercise class and immediately following it. Participants in CR-Only also provided the two blood draws in the morning, with a 1-h rest between the draws. All participants were monetarily compensated for completing study assessments and providing blood draws, but not for attending the interventions. Recruitment began April 28, 2015 and the last study assessment was completed October 13, 2017 following attainment of the planned sample size.

1.7. Statistical analysis

Two prior studies of severe mental illness examined the effects of adding exercise to cognitive remediation versus cognitive remediation alone on cognition, one of which found a large effect size for exercise (Nuechterlein et al., 2016) and the other which reported mixed effects favoring exercise (Oertel-Knöchel et al., 2014). Based on this research we determined sample size to detect a medium effect size. Using G*Power with $p < .05$ and assuming a correlation of 0.5 between the two cognitive composite score assessments, the power to detect a medium effect size of the time by group interaction for a repeated measures ANOVA ($f = 0.26$) was 0.80 for a sample size of 30 study completers.

Differences between the treatment groups on all baseline measures were evaluated by computing χ^2 analyses and *t*-tests. Participation in the cognitive remediation and exercise interventions was determined by computing the percentage of subjects in each group who were "exposed" to each intervention (completed ≥6 sessions) and the mean number of sessions attended. Activity levels of participants in the two groups over the study period were compared by conducting *t*-tests on the mean number of steps recorded on Fitbits for study days and non-study days.

All outcome analyses were intent-to-treat, including all participants with available data regardless of their participation in the study interventions. To evaluate whether CR + E participants improved more in cognition or depression from baseline to post-treatment than CR-Only, general linear models were fit on the cognitive composite score, individual cognitive tests, and MADRS. For these analyses, the time effect tests whether both groups improved over time and the group by time interaction tests the exercise treatment effect.

Changes in BDNF between the two treatment groups were evaluated two ways. First, to determine whether CR + E participants increased more in BDNF from pre to post exercise at Week-5 and Week-10 than CR-Only, general linear models were fit on the BDNF change scores at each assessment, with group as the independent variable and baseline BDNF as a covariate. The group effect tests whether CR + E participants increased more in BDNF following exercise at Weeks 5 and 10 than CR-Only, whereas the group by time interaction tests whether the groups differed significantly in BDNF changes over time. Second, to evaluate whether the groups differed in change in resting BDNF over time, general linear models were performed on baseline BDNF and resting BDNF at Weeks 5 and 10, with group as the independent variable. The group by time interaction tests whether resting BDNF increased more for CR + E participants than CR-Only.

These planned analyses were followed by exploratory analyses to evaluate whether baseline BDNF predicted improvements in cognitive functioning following cognitive remediation or moderated the effects of exercise on cognition. BMI was included as a covariate based on evidence that higher BMI is associated with worse cognitive functioning in schizophrenia (Hidese et al., 2018; Kimhy et al., 2014) and reduced BDNF in mixed psychiatric and control groups (Pillai et al., 2012). Group and baseline BDNF were the independent variables, post-treatment cognitive scores were the dependent variables, and the corresponding baseline cognitive scores (and BMI) were covariates. For these analyses, the main effect for baseline BDNF tests whether it predicts improvement in cognitive functioning following cognitive remediation across both groups, and the BDNF by group interaction tests whether baseline BDNF moderated the impact of exercise on cognitive functioning at post-treatment.

2. Results

Table 1 provides the baseline characteristics of the two groups. The mean age of the participants was 40.11 years old, with the majority men (58%), never married (79%), not currently employed (97%), and with a schizophrenia-spectrum diagnosis (65%). The average total BPRS score was 44.44, which corresponds to a "moderate" level of symptom severity (Leucht et al., 2005). Comparisons of the CR + E and CR-Only groups on baseline measures indicated no significant ($p < .05$) differences.

2.1. Participation in study interventions

The average number of cognitive training sessions attended by participants in CR-Only was 22.13 (SD = 7.41) and for CR + E it was 21.53 (SD = 7.51). The average number of exercise classes attended by CR + E participants was 21.47 (SD = 7.64). Among the 17 participants in CR-Only, 13 (76.4%) attended ≥6 sessions and were "exposed" to the intervention. Of the 17 participants in CR + E, 15 (88.2%) attended ≥6 cognitive remediation sessions and the same number attended ≥6

Table 1
Participant characteristics by treatment groups: Cognitive remediation and exercise (CR + E) and cognitive remediation only (CR-Only).

Categorical Variables	CR + E (N = 17)		CR-Only (N = 17)	
	N	%	N	%
Gender				
Male	11	64.71%	9	52.94%
Female	6	35.29%	8	47.06%
Ethnicity				
Hispanic/Latino	0	0%	3	17.65%
Not Hispanic/Latino	17	100%	14	82.35%
Race				
White	7	41.18%	6	35.29%
Black or African American	8	47.06%	4	23.53%
Asian	2	11.76%	3	17.65%
American Indian or Alaska Native	0	0%	1	5.88%
Other	0	0%	3	17.65%
Diagnosis				
Schizophrenia	7	41.18%	5	29.41%
Schizoaffective Disorder	4	23.53%	5	29.41%
Schizophreniform Disorder	1	5.88%	0	0%
Bipolar I Disorder	3	17.65%	6	35.29%
Bipolar II Disorder	2	11.76%	1	5.88%
Medication				
Antipsychotics	12	70.59%	12	70.59%
Antidepressants	5	29.41%	4	28.57%
Mood Stabilizers	3	17.65%	7	41.18%
Benzodiazepines	3	17.65%	5	29.41%
Beta-blockers	2	11.76%	0	0%
Marital Status				
Married/Living with Partner	0	0%	2	11.76%
Divorced/Separated/ Widowed	3	17.65%	2	11.76%
Never Married	14	82.35%	13	76.47%
Education				
Did Not Complete High School	0	0%	1	5.88%
Completed High School/GED	4	23.53%	2	11.76%
Some College/ Associates Degree	9	52.94%	10	58.82%
Completed College	3	17.65%	2	11.76%
Graduate Degree	1	5.88%	2	11.76%
Work Status				
Currently Working	0	0%	1	5.88%
Unemployed	17	100%	16	94.12%
Living Status in Community				
Independent-alone	5	29.41%	8	47.06%
Independent-with unrelated others	0	0%	2	11.76%
With family	11	64.71%	5	29.41%
Group home	1	5.88%	2	11.76%
Smoking Status				
Yes	7	41.18%	5	29.41%
No	10	58.82%	12	70.59%
IPAQ Activity Level				
Low Activity	8	47.06%	9	52.94%
Moderate Activity	6	35.29%	7	41.12%
High Activity	3	17.65%	1	5.88%
Hospitalizations in Last Two years				
Yes	9	52.94%	5	29.41%
No	8	47.06%	12	70.59%
	Mean (SD)	Range	Mean (SD)	Range
Age	36.94 (12.72)	20–58	43.29 (10.64)	24–61
BMI at Baseline (kg/m^2)	27.66 (5.07)	19.10–35	28 (5.17)	19.10–37.20
Average Cholinergic Load of Medication	2.33 (0.98)	1–3	1.71 (0.91)	1–3
Self-Reported Physical Health	2.70 (1.10)	1–4	3.06 (0.83)	2–3
IPAQ MET score	1164.26 (1347.92)	0–4860	908 (1081.30)	0–4158
Number of Hospitalizations in Past Two Years	1.18 (1.24)	0–3	1.4 (0.54)	0–2
BPRS Total	44.82 (12.54)	29–76	44.06 (7.81)	30–57
Depression/Anxiety	2.23 (0.84)	1–3.67	2.74 (0.92)	1.33–4.67
Activation	1.47 (0.67)	1–3.14	1.40 (0.49)	1–2.71
Retardation	1.69 (0.76)	1–3.40	1.46 (0.46)	1–2.40
Psychosis	2.20 (1.46)	1–5.75	2.02 (1.07)	1–4.20
WRAT Standard Score	97.35 (11.78)	75–117	96.12 (9.82)	73–111
MADRS Total	13.24 (8.43)	1–32	14.35 (7.79)	1–29

exercise classes and were thus exposed to each intervention.

2.2. Activity levels

The *t*-test comparing the two groups on number of steps taken by participants on study days was significant ($t = 2.34$, $df = 24$, $p < .03$), indicating participants in CR + E took more steps ($M = 9211.14$, $SD = 3019.19$) than those in CR-Only ($M = 6788.78$, $SD = 2085.68$). The *t*-test comparing the groups on steps taken on non-study days was not significant ($Ms = 6821.01$, 6053.01, respectively).

2.3. Changes in cognitive functioning and depression

The results of the general linear model analyses evaluating changes in cognitive functioning for the two groups from baseline to post-treatment are summarized in Table 2. Significant time effects indicating improved performance were found for the cognitive composite score and 8 of 11 individual cognitive tests. HVLT-delayed did not change, whereas performance on NAB Mazes declined. This decline may be an artifact of the cognitive remediation approach in which strategy coaching on similar maze exercises in Cogpack focuses on reducing errors rather than improving speed (McGurk and Mueser, 2021), whereas performance on the Mazes test is based on time to complete mazes regardless of errors. None of the group by time interactions were significant, indicating similar cognitive improvements for both groups. However, there was a trend for participants in CR + E to improve more in Trails B than those in CR-Only (moderate effect size partial eta-squared = .10).

Neither the time nor group by time interaction effects for changes in the MADRS were significant, indicating stable levels of depression over the study for both groups.

2.4. Changes in BDNF

Pearson correlations between the different BDNF measures at each of the assessment points are displayed in Table 3. Total BDNF was moderately correlated with Mature BDNF (median $r = 0.559$) and Mature:Total BDNF ratio (median $r = 0.526$), while the correlations between Mature BDNF and Mature:Total BDNF ratio were lower (median $r = 0.453$).

Descriptive statistics for the BDNF measures at each assessment are provided in Table 4. The general linear regression model evaluating whether CR + E participants increased more in BDNF following exercise at Weeks 5 and 10 than CR-Only indicated no group, time, or group by

Table 2
Cognitive changes for each cognitive test (T-scores) by intervention group: Cognitive remediation and exercise (CR + E) and cognitive remediation only (CR-Only).

Cognitive Variable	N	M (SD)	N	M (SD)	df	F	p	Partial Eta-Squared	df	F	p	Partial Eta-Squared
Trail Making Test, Part A					1	19.584	.000	.430	1	.010	.921	.000
CR + E	17	37.41 (10.58)	14	48.07 (7.89)								
CR-Only	17	37.24 (10.92)	14	43.36 (10.29)								
Trail Making Test, Part B					1	25.080	.000	.491	1	2.935	.099	.101
CR + E	17	21.14 (20.02)	14	33.79 (18.22)								
CR-Only	17	20.06 (19.53)	14	45.43 (17.49)								
Symbol Coding					1	6.019	.021	.188	1	2.043	.165	.073
CR + E	17	30.47 (11.25)	14	34.5 (17.19)								
CR-Only	17	35.47 (11.88)	14	41.5 (11.88)								
HVLT Sum					1	10.934	.003	.296	1	.509	.482	.019
CR + E	17	37.65 (10.09)	14	43.71 (10.79)								
CR-Only	17	36.94 (6.59)	14	42.21 (9.52)								
HVLT- D					1	1.251	.274	.048	1	.155	.697	.006
CR + E	16	34.31 (14.7)	14	39.21 (12.6)								
CR-Only	17	36.53 (14.9)	14	39.79 (14.9)								
Letter-Number Span					1	4.251	.049	.141	1	.037	.849	.001
CR + E	17	41.53 (8.55)	14	46 (9.64)								
CR-Only	17	37.29 (11.33)	14	42 (10.8)								
Mazes Test					1	4.338	.047	.143	1	.156	.696	.006
CR + E	17	39.12 (8.07)	14	36.21 (3.17)								
CR-Only	17	40.24 (12.05)	14	37.64 (6.1)								
BVMT- Sum					1	9.015	.006	.257	1	.006	.799	.003
CR + E	17	29.18 (10.03)	14	35.43 (9.19)								
CR-Only	17	34.06 (9.27)	14	40.57 (10.04)								
BVMT-D					1	4.908	.036	.164	1	.389	.538	.015
CR + E	16	29.56 (14.75)	14	37.57 (14.42)								
CR-Only	17	31.24 (11.93)	14	41.5 (13.63)								
Category Fluency					1	10.303	.004	.292	1	.280	.601	.011
CR + E	17	40.41 (10.7)	13	44 (9.5)								
CR-Only	17	44.76 (6.74)	14	48 (7.77)								
CPT					1	8.416	.008	.252	1	.104	.750	.004
CR + E	17	37.18 (13.22)	13	43.15 (13.42)								
CR-Only	17	41.41 (11.64)	14	47.29 (12.5)								
Composite Cognitive					1	45.764	.000	.638	1	.704	.409	.026
CR + E	17	33.85 (6.64)	13	40.15 (5.01)								
CR-Only	17	34.06 (8.01)	14	42.66 (3.15)								

Table 3
Correlations between different BDNF measures at corresponding time points.

		N	BDNF at Corresponding Time Points	
			BDNF Total	BDNF M:T Ratio
Baseline	BDNF Mature	36	.575**	.479**
	BDNF M:T Ratio	36	-.401*	
Pre-ExWeek 5	BDNF Mature	31	.682**	.025
	BDNF M:T Ratio	31	-.670**	
Post-Ex Week 5	BDNF Mature	30	.539**	.463**
	BDNF M:T Ratio	30	-.465**	
Pre-ExWeek 10	BDNF Mature	29	.389*	.453*
	BDNF M:T Ratio	29	-.551**	
Post-Ex Week 10	BDNF Mature	28	.559**	.328
	BDNF M:T Ratio	28	-.526**	

Note: *$p < .05$, **$p < .01$.

time interactions for all three BDNF measures. Similarly, the general regression analysis examining changes in resting BDNF from baseline to Week 5 and Week 10 revealed no main or interaction effects. Thus, resting BDNF did not change over the course of the study for either group, nor did the CR + E group increase more in BDNF following exercise at Weeks 5 and 10 than CR-Only.

2.5. Exploratory moderation analyses

The linear regression analyses evaluating whether baseline BDNF moderated improvements in cognitive functioning following cognitive remediation, or moderated the added effects of exercise (controlling for BMI) are summarized in Supplement Table 1. None of the main effects of BDNF predicting change in cognition were significant, suggesting BDNF did not moderate the effects of cognitive remediation. Two analyses revealed significant BDNF by group interactions on cognitive outcomes: Mature BDNF on Mazes, and Mature:Total BDNF ratio on Fluency. For both analyses, the effects of exercise (CR + E) were stronger in participants who had lower baseline BDNF levels than higher levels.

Table 4
Means and standard deviations of different BDNF measures at each time point by intervention group: Cognitive remediation and exercise (CR + E) and cognitive remediation only (CR-Only).

		Baseline		5 Weeks				10 Weeks			
		N		N	Pre-Ex	N	Post-Ex	N	Pre-Ex	N	Post-Ex
Total BDNF (pg/ml)	CR-Only	16	47.35 (7.26)	13	45.73 (12.71)	12	47.00 (10.07)	12	46.03 (10.96)	11	48.30 (10.46)
	CR + E	17	48.97 (19.52)	16	52.00 (23.13)	16	50.80 (20.86)	15	54.09 (26.70)	15	53.91 (22.66)
Mature BDNF (pg/ml)	CR- Only	16	28.84 (7.73)	13	32.34 (5.06)	13	27.77 (8.96)	12	31.06 (9.72)	12	30.27 (10.13)
	CR + E	17	29.33 (8.72)	15	30.98 (9.64)	15	30.74 (8.40)	15	31.03 (8.35)	15	32.35 (9.78)
BDNF M:T Ratio	CR- Only	16	.61 (.15)	13	.73 (.14)	12	.63 (.22)	12	.70 (.22)	11	.70 (.22)
	CR + E	17	.63 (.16)	15	.64 (.16)	15	.64 (.16)	15	.63 (.17)	15	.64 (.20)

Supplement Figure 1 depicts these interactions, based on median splits of baseline BDNF for the total group.

Although baseline BMI did not interact with BDNF or treatment group in preliminary analyses (and interaction terms were dropped), BMI was a significant predictor of cognitive gain in the moderator analyses. Specifically, higher BMI predicted less improvement in the cognitive composite score, and on Trails B, Symbol Coding Synbom, and Letter-Number Span. Using a cut-score of BMI ≥30 kg/m^2 to divide participants into obese (n = 12) or non-obese (n = 22) groups, the association between BMI and improvement in composite cognitive score is depicted in Fig. 2.

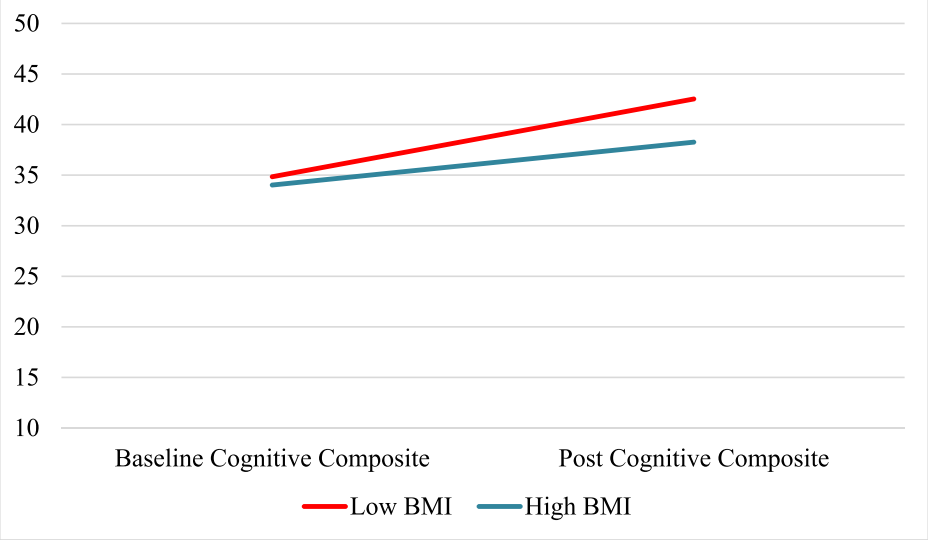
3. Discussion

Adding an aerobic exercise program to an equally intensive cognitive remediation program did not lead to greater improvements in cognitive functioning compared to cognitive remediation alone in this sample of participants with severe mental illness. Rather, both groups improved on overall cognitive functioning and most of the individual neurocognitive tests. The lack of effect of exercise on improving the impact of cognitive remediation occurred despite strong implementation of the experimental interventions, as reflected by the high engagement of participants in both groups. Furthermore, Fitbit trackers showed that participants in CR + E took significantly more steps on the three weekly study days (but not non-study days) of the 10-week study than those in CR-Only, independently verifying the higher activity level of the CR + E group. The findings did not support the hypothesis that exercise augments the effects of cognitive remediation in this population.

These findings differ from two other studies suggesting that exercise increases the effects of cognitive remediation in this population (Nuechterlein et al., 2016; Oertel-Knöchel et al., 2014). An important difference between the studies is the effectiveness of the cognitive remediation program alone at improving cognitive functioning, as the less potent the program the greater potential for exercise to enhance cognitive performance. In Nuechterlein et al. (2016) the cognitive remediation only group actually *declined* slightly from pre-treatment to post-treatment on the MCCBS, and thus there was no cognitive remediation effect for exercise to augment. In Oertel-Knöchel et al. (2014) the results were mixed, with participants in the cognitive remediation only intervention showing moderate within group effect sizes for gains in two cognitive domains (speed of processing and visual learning) and small effect sizes for the other two domains (working memory and verbal learning). The relatively limited effects of cognitive remediation in Oertel-Knöchel et al. may be due in part to the limited amount cognitive training in the program (90 min/week for 4 weeks). In contrast, the longer and more intensive cognitive remediation program in present study (3 h/week for 10 weeks) had robust effects on improving cognitive functioning, with large effect sizes across both groups on 9 of the 11 cognitive subscales, as well as the cognitive composite score (based on partial eta-squared, see Table 2). Thus, the greater effectiveness of the cognitive remediation program in this study may have limited the extent to which added exercise could further improve cognitive outcomes.

That BMI was a potent moderator of the cognitive effects of cognitive remediation is an intriguing finding. Despite the relatively restricted range of BMI in study participants, higher BMI was associated with reduced cognitive gains in overall cognition, and in cognitive flexibility, processing speed, and verbal working memory. These cognitive areas have been shown to be adversely impacted by obesity or the metabolic syndrome in persons with schizophrenia (Bosia et al., 2018; Boyer et al., 2013) and in the general population (Loprinzi and Frith, 2018; Wang et al., 2016; Yates et al., 2012). Obesity-related mechanisms postulated to impair cognition include interference with the neural mechanisms of learning and memory, including reduction of BDNF and inhibition of long-term potentiation. Research evaluating the potential moderating role of obesity or metabolic syndrome in cognitive enhancement would be informative, especially given their prevalence in persons with severe mental illness.

It is unclear why exercise in this study had no effect on the BDNF measures, including greater increases in resting BDNF from baseline to Weeks 5 and 10 or greater increases in BDNF after exercise at those weeks. A prior meta-analysis of exercise and BDNF studies in the general population (Szuhany et al., 2014) indicated a small effect size for exercise on increasing resting BDNF (Hedge's g = 0.27), and a moderate effect size for increased BDNF following a bout of exercise during a program of regular exercise (Hedge's g = 0.59). Although many studies have reported alterations in peripheral (serum or plasma) BDNF levels in schizophrenia, data are inconsistent, with the majority reporting lower serum BDNF levels compared to healthy controls (Green et al., 2011; Pandya et al., 2012), but some reporting higher serum BDNF levels (Reis et al., 2008; Weickert et al., 2019). A limitation of this study is the lack of data on whether baseline BDNF levels of participants significantly differed from healthy controls, a comparison that is complicated by



Note: F = 4.896, p = .036

Fig. 2. Cognitive Composite Scores at Baseline and Post Intervention by BMI split at Obese Level (BMI ≥30 kg/m^2). Note: F = 4.896, p = .036.

studies suggesting that peripheral BDNF levels increase following antipsychotic medication (Grillo et al., 2007; Lee and Kim, 2009). Further, exercise has been shown to differentially regulate BDNF levels in serum and plasma samples (Máderová et al., 2019). We cannot rule out the possible role of changes in plasma BDNF on cognitive remediation in this study.

It is possible that the method of recruiting participants for the study through referrals and fliers resulted in a sample that was more motivated and more physically active than typical persons with severe mental illness receiving community-based treatment. Another limitation was the lack of longer term patient-centered outcomes such as quality of life, health, and symptoms that may have demonstrated benefits of the supplementary exercise program. Finally, an important limitation of this study was the modest sample size resulting in limited statistical power to test the hypothesized effects of supplementing cognitive remediation with exercise on both BDNF levels and cognitive functioning. Further research on this topic is warranted.

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Appendix A. Supplementary data

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