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The synergistic benefits of physical and cognitive exercise in schizophrenia: Promoting motivation to enhance community effectiveness

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ABSTRACT

Emerging research highlights the potential cognitive benefits of physical exercise (PE) programs for schizophrenia (SCZ). The few recent efficacy studies that examined augmenting cognitive training (CT) with PE suggest superior effects of the combination. The next step is to consider strategies to enhance adherence in real-world settings if this type of combined treatment is going to be effective. We present the first community effectiveness data for PE and CT that included a motivationally-enhancing, self-determined approach to exercise, in lieu of participant payment. Eighty-five outpatients with schizophrenia attending an intensive outpatient program were randomized to 18 h of either (A) self-determined PE regimen with choice from a menu of different activities; (B) tablet-based neurofeedback CT focused on processing speed (PS) and working memory (WM), or (C) a time-matched combination of PE and CT. Assessments were conducted at baseline, post, and follow-up (2 mo). All groups improved in WM from baseline to post, with greatest gains in the PE only group. At follow-up, cognitive gains originally observed in the PE-only group disappeared, while the PE + CT group evidenced improvements in WM and psychotic symptoms. Notably, attrition for PE was only 7%. Our data shows that combining PE and CT leads to lasting effects that are superior to those of either intervention alone. The low PE drop-out rate suggests a self-determined approach to the exercise regimen was tolerable, and may be an important component of future community implementation efforts.

1. Introduction

Cognitive impairments are a hallmark feature of schizophrenia (SCZ) and have been shown to impact functional outcomes (Reddy et al., 2016; Twamley et al., 2017). Efforts at improving cognition in this population have focused on cognitive training (CT), an efficacious method with medium effect sizes on various cognitive outcomes (Kurtz, 2015; Vinogradov et al., 2012; Wykes et al., 2011). In an attempt to bolster the efficacy of CT in SCZ, several recent studies have examined the combined effects of physical exercise (PE) and CT. There is a large literature in support of the positive cognitive impact of PE on cognition in non-psychiatric samples (Chang et al., 2012; Smith et al., 2015; Taylor (Parker) et al., 2011). While there has been relatively less research on the impact of PE interventions in individuals with SCZ, these data are also promising, with positive effects noted for cognition (global, memory, processing speed) and both positive and negative symptoms (Firth et al., 2015, 2017; Kimhy et al., 2015; Malchow et al., 2013; Vakhrusheva et al., 2016).

The few studies that have examined augmenting CT with PE in people with SCZ suggest that the combination may offer greater cognitive and negative symptom benefits than CT alone (Malchow et al., 2015; Nuechterlein et al., 2016; Oertel-Knöchel et al., 2014). However, while these efficacy studies have been promising, their real-world applicability has been diminished by high attrition/poor compliance to the PE interventions or limited translation to community effectiveness due to need for monetary rewards to achieve compliance.

Studies by Scheewe et al. (2013a, 2013b) and a review by Firth et al. (2015) clearly highlighted the importance of treatment compliance in

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physical activity interventions, as only SCZ patients who completed a minimal level of exercise (i.e. 50% of the program) showed improvement in cardiorespiratory fitness and hippocampal plasticity. However, participants in these studies were paid to exercise, and even with this incentive, only 65–68% of SCZ samples were considered treatment completers using the generous cutoff. Based on this, researchers have recommended that exercise interventions should ultimately include therapeutic approaches that address motivation for PE, as paying individuals to exercise is unlikely to be feasible in community effectiveness trials or on an individual treatment basis (Taylor and Pescatello, 2016; Yoon et al., 2016).

Improving compliance and adherence also remain a significant concern in CT programs. Whereas laboratory-based evaluations of CT indicate efficacy along with high treatment compliance (with nearly all studies noting how participants were paid to attend treatment sessions, and with the standard practice of reminder calls and other outreach efforts to increase compliance), the real-world effectiveness of CT can be compromised by amotivation since patients are not paid to participate in CT offered as part of clinical care (Kremen et al., 2016; Medalia et al., 2019; Wykes and Spaulding, 2011). For example, a recent report of the effects of an intensive community outpatient psychosocial rehabilitation program for SCZ offering CT along with structured skills groups, such as social skills training, vocational counseling, and physical exercise, indicated that 37% of those enrolled (47 of 127) dropped out within the first month of treatment (Kurtz et al., 2015). These attrition rates for clinical programs stand in stark contrast to laboratory-based efficacy studies of CT with attrition rates from 10 to 20% (Kurtz, 2015).

Researchers evaluating exercise interventions in SCZ have called for new work to focus on approaches to enhance exercise motivation and increase attendance, in order to ensure an adequate dose of the intervention to test efficacy. Excellent examples of how this can be done have been published by Beebe et al. (2011) and Yoon et al. (2016), where the clinical feasibility of group-based, outdoor cycling or walking programs focused on improving motivation and enjoyment for exercising. The central elements of their exercise programs were individualized goals and patient preferences for how to exercise. Here we see a divergence from the *prescribed* exercise regimens in previous PE trials, where participants did not have input about their exercise program. While earlier PE studies with prescribed exercise regimens struggled with poor compliance and high attrition, Yoon and Beebe reported considerably lower attrition rates (<8.4%), suggesting that motivational enhancements can be successful.

Failure to address adherence problems at the beginning stages of treatment development can have significant consequences once a laboratory intervention progresses to the effectiveness stage, potentially necessitating drastic changes to the intervention parameters or methods to retain participants (Medalia et al., 2019). While research on augmenting CT with PE is still in its' early stages, it was for this reason our group has focused on developing and evaluating methods to promote engagement for both physical and cognitive exercise in a community setting, without payment for participation, as such is often not feasible in community settings. Data presented herein were derived from a program evaluation intended to inform whether this intervention should be added to the curriculum of other offerings in an intensive outpatient schizophrenia program.

2. Methods

2.1. Participants

Program data was obtained for 85 participants attending the intensive outpatient Schizophrenia Rehabilitation Program (SRP) at Hartford Hospital's Institute of Living. Each successive new admission who was allowed to participate in physical or cognitive exercise by their referring psychiatrist was randomly allocated to one of the treatment groups. Participant characteristics were (a) chart diagnosis of schizophrenia or schizoaffective disorder, (b) compliant with their psychotropic regimen for at least 8 weeks prior to SRP admission with no changes in medications, (c) no history of neurologic illness, (d) no stage I or higher blood pressure (>140/90 mm Hg), and (e) no osteoarthritis or orthopedic issues affecting gait.

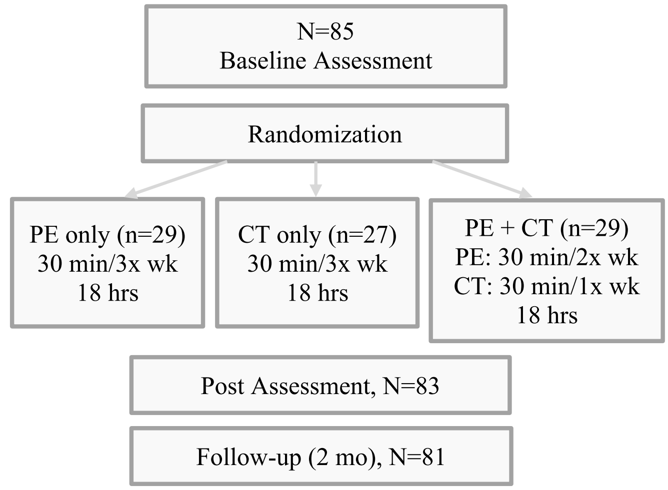

Fig. 1. Study design.

2.2. Procedures

Physical and cognitive exercise treatments described herein were administered by clinical staff and were a standard part of the intensive outpatient rehabilitation program. In order to reduce potential effects of clinical bias, the SRP program director elected to allow for random assignment to the three treatment options. Patients who were newly admitted to the program and who chose to participate in psychosocial programming were randomly allocated after intake (1:1:1 ratio) to three months (18 h total) of: a) PE only, or b) CT only, or c) PE + CT (see Fig. 1). PE was conducted by SRP program staff three times per week on Monday, Wednesday, and Fridays from 10 to 10:30 am while CT was provided shortly after, from 11 to 11:30 am. Those in the PE + CT group did PE on Mondays and Fridays and CT on Wednesdays. The three conditions did not differ in treatment dose or duration. Separate program staff, who were not blind to treatment allocation, conducted assessments of cognition, symptoms, and motivation at intake, immediately post-treatment (3 months), and at 2-month follow-up (5 months after intake). No payment was provided for participating in the treatment sessions or assessments since this was all part of standard intensive outpatient clinical care. During the follow-up period, other standard intensive outpatient treatment continued. Permission to conduct and extract clinical data for purposes of this paper was approved by the local institutional review board.

2.3. Interventions

2.3.1. Physical exercise

At the start of each PE session, participants chose from a menu of loosely supervised group PE activities. These included aerobic exercises such as the treadmill, elliptical and rowing machines, and stationary bikes, weight training using nautilus equipment and free weights, and outdoor activities such as basketball or power walking around the campus. Each activity included individually tailored exercise goals (e.g. 15 min on exercise bikes at level 6) so that participants would reach volitional exhaustion—a commonly accepted physiological gauge of strenuous exercise (Schlader et al., 2011)—at least twice per week as defined by 3 min at target heart rate (220 − age × 60–90%).

For aerobic and weight training, the duration of each exercise session was progressively increased from 10 to 20 min during the first four weeks under the guidance of an exercise trainer. Once participants were able to perform 20 min of aerobic exercise, they continued this amount of exercise for the remainder of their participation. An additional 5 min of warm-up and 5 min of cool-down exercises were included so that each workout comprised 30 min. For power walking, distance and pace was set and titrated according to pre-determined maximal heart rates. For all PE sessions, participants exercised at between 60 and 85% of their maximal aerobic fitness using their pre-determined maximal heart rate to regulate exercise intensity. Heart rate monitors and accelerometers were used to monitor heart rate and dosage and intensity of PE.

Importantly, individuals exercised on their own in these loosely monitored groups. Once the exercise trainer provided the exercise venue (i.e. opened the door to the gym and provided basketballs) and/or suggested the duration/level of exercise at the beginning of each session (i.e. 10 min on exercise bike), the trainer then only monitored the exercise with minimal interactions with individual patients.

2.3.2. PE engagement

According to Self Determination Theory (SDT), the most widely accepted and applied theory of motivational science in humans (Ryan and Deci, 2000), a sense of control and autonomy must be present in order for someone to be motivated for a particular task, especially when no external reinforcement is available (Williams et al., 2006). This is especially pertinent, according to SDT, when the individual may not understand the value of the activity due to a lack of insight and/or cognitive deficits, has difficulty following through or persisting on everyday tasks, lacks the motivation to initially attempt the activity, and/or experiences apathy (Deci and Ryan, 2008)—all issues common to SCZ. Hence, we offered activity choices as a simple but empirically robust method to instill a sense of control and personalize the treatment. To date, no PE + CT study—and no PE study in SCZ except for the recent study by Yoon et al. mentioned above—has taken advantage of this method to improve compliance to PE.

2.4. Cognitive training (processing speed and WM)

At the start of each group CT session, participants chose from a menu of Android-tablet delivered tasks, that were designed to specifically hone visual scanning efficiency by targeting and correcting scan paths (how the person tracks a target on a screen). These tasks provide practice in inhibiting the selection of non-essential targets, holding target information in working memory, and discriminating figure-ground details based on recalled information. Unlike most CT programs which adjust difficulty purely based on performance, our CT program augmented this approach with pupillometric cognitive load information. This program had been developed by our team and initially piloted in healthy controls, teenagers and young adults at risk for psychosis, and in individuals with schizophrenia, as a method to improve processing speed and working memory (Choi et al., 2017).

2.4.1. CT engagement

Our investigations in CT have used pupillometry as a neurobiological gauge of task engagement and cognitive resource load when working on CT tasks. Pupil dilation is a barometer of sympathetic nervous system load. It reveals underlying neurophysiologic engagement that serves as a precursor to a decline in motivation for behavioral tasks (Granholm et al., 2007, 2015). In this way, pupillometry provides a broad indication of how much an individual is motivated and actively involved in a task at that very moment. Pupillometry allowed us to optimize the training exercises by providing immediate biofeedback to the training software that then automatically adjusts training task parameters for a personalized and efficient training program. Moreover, a pupillometry provided a broad indication of how much the person was actively involved in the exercise at that very moment, even before performance was registered as a correct or incorrect response. This is important because if CT only uses performance feedback and the person is making numerous errors, there is a risk of the person disengaging from the program. By manipulating the CT task based on this neurobiological parameter and contextualizing the learning cues based on participant choices to make CT enjoyable (patient-determined gaming themes), we have previously found that this approach—compared to CT without pupillometry—promoted greater cognitive benefits in processing speed and working memory, greater perceived self-competency and, most importantly, higher levels of task-specific motivation to attempt the demanding CT tasks. Together, we have found these to then translate to less attrition and greater treatment compliance (Choi et al., 2017).

2.5. Measures

Working memory and processing speed were measured using the Working Memory Index (WMI) and Processing Speed Index (PSI) of the Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV; Wechsler, 2014). Symptoms were gauged with the Brief Psychiatric Rating Scale (BPRS; Lukoff et al., 1986; Ventura et al., 2000). Motivation for PE and CT was assessed at baseline using the Intrinsic Motivation Inventory for Schizophrenia Research (IMI-SR; Choi et al., 2010). Treatment compliance and adherence were operationalized as the average number of treatment sessions attended and the percentage of participants in each of the three conditions who completed all treatment sessions, respectively. A Lintelek Fitness Tracker® or CanMixs Fitness Tracker® was worn by participants during the exercise sessions to assess continuous heart rate as well as light, moderate, and vigorous physical activity.

2.6. Data analysis

Analyses were intent-to-treat and included data from all 85 participants randomized to PE, CT, or PE + CT arms. The distribution of scores for each variable in each group was inspected for normality and compared to relevant comparison groups for homogeneity of variance. Demographic and other baseline measures were compared across the three groups using one-way analysis of variance (ANOVA). To assess the impact of PE or CT or PE + CT on working memory, processing speed, and symptoms, we computed change scores from pre- to post-training for each participant on respective WAIS indices and the BPRS. We then entered these change scores into three one-way ANOVAs, with experimental condition as a between-subjects variable.

To assess the durability of change in cognition and symptoms as a function of the treatment, we computed a second set of change scores between test performance at intervention termination and performance at the two-month follow-up for each participant on each measure. Again, these change scores were entered into one-way ANOVAs with treatment condition as a between-subjects variable. When significant effects were evident in ANOVA, Tukey's HSD test was used for pair-wise comparisons.

To estimate the degree of change in working memory, processing speed, and symptoms between those with low or high task motivation for the activity (PE, CT, or PE + CT), a point-biserial correlation was calculated between high-low baseline motivation and residual change scores from baseline to post for each of the three conditions. High/low baseline motivation was determined based on median split on the Intrinsic Motivation Inventory. All statistical tests were two-tailed and alpha was set at 0.05.

3. Results

There were no significant baseline group differences on demographic, clinical, symptom, or cognitive variables (see Table 1). While approximately 17% of participants chose to do the same physical

Table 1
Demographic and baseline clinical characteristics of the three groups.

	PE only n = 29	CT only n = 27	PE + CT n = 29	F value	Significance (p value)
Age (years)	34.37 (6.04)	35.18 (6.72)	34.47 (7.05)	0.12	.88
Education (years)	11.04 (2.42)	11.51 (3.02)	11.60 (3.17)	0.31	.73
Male (%)	59	49	52	Chi-sq = 0.93	.06
Duration of illness (yrs)	12.37 (6.81)	12.06 (7.23)	13.02 (7.97)	0.12	.88
Percentage on atypical antipsychotics	91	94	91	Chi-sq = 0.28	.58
Schizoaffective (%)	58	56	55	Chi-sq = 0.62	.21
Working memory					
WAIS WMI	83.63 (9.05)	81.48 (10.21)	81.77 (8.97)	0.44	.65
Processing speed					
WAIS PSI	74.34 (11.84)	72.61 (12.35)	72.88 (11.22)	0.18	.84
BPRS (symptoms)					
Positive factor	31.34 (9.12)	29.76 (6.36)	29.52 (10.02)	0.37	.69
Negative factor	15.98 (6.78)	13.79 (4.11)	13.55 (3.43)	2.05	.13
Agitation-mania	14.38 (5.73)	15.02 (6.34)	17.18 (6.76)	0.81	.12
Depression-anxiety	18.75 (8.68)	19.03 (6.21)	17.27 (7.19)	0.46	.63
Total	60.02 (17.24)	58.19 (13.39)	58.46 (19.20)	0.10	.91
Completed entire study intervention (%)	93	96	93		

activity nearly every single session, the rest chose different activities every week or every treatment day. Of note, even without external reinforcement to attend each session, 96% in the CT condition and 93% in the PE or PE + CT conditions completed all of the sessions.

As shown in Fig. 2, the one-way ANOVA for change on the WAIS WMI from pre- to post-training revealed a main effect of group ($F [2, 81] = 11.40$, $p < .01$) with PE and PE + CT conditions both producing similar improvement in working memory relative to CT only ($p < .001$). We also found a main effect of group on WAIS PSI from pre- to post-training change ($F [2, 81] = 14.78$, $p < .001$), with PE producing significant improvement in processing speed relative to CT and PE + CT (p's < .001), with no significant differences between CT and PE + CT.

To assess durability, change scores from post to the 2-month follow-up were assessed (see Fig. 2). There were significant group effects in changes in WAIS WMI and PSI during the follow-up ($F [3, 78] = 22.19–23.81$, p's < .001), with gains in working memory and processing speed maintained over the follow-up interval only in the PE + CT group.

While there was a pre-post decline on BPRS Negative Symptoms

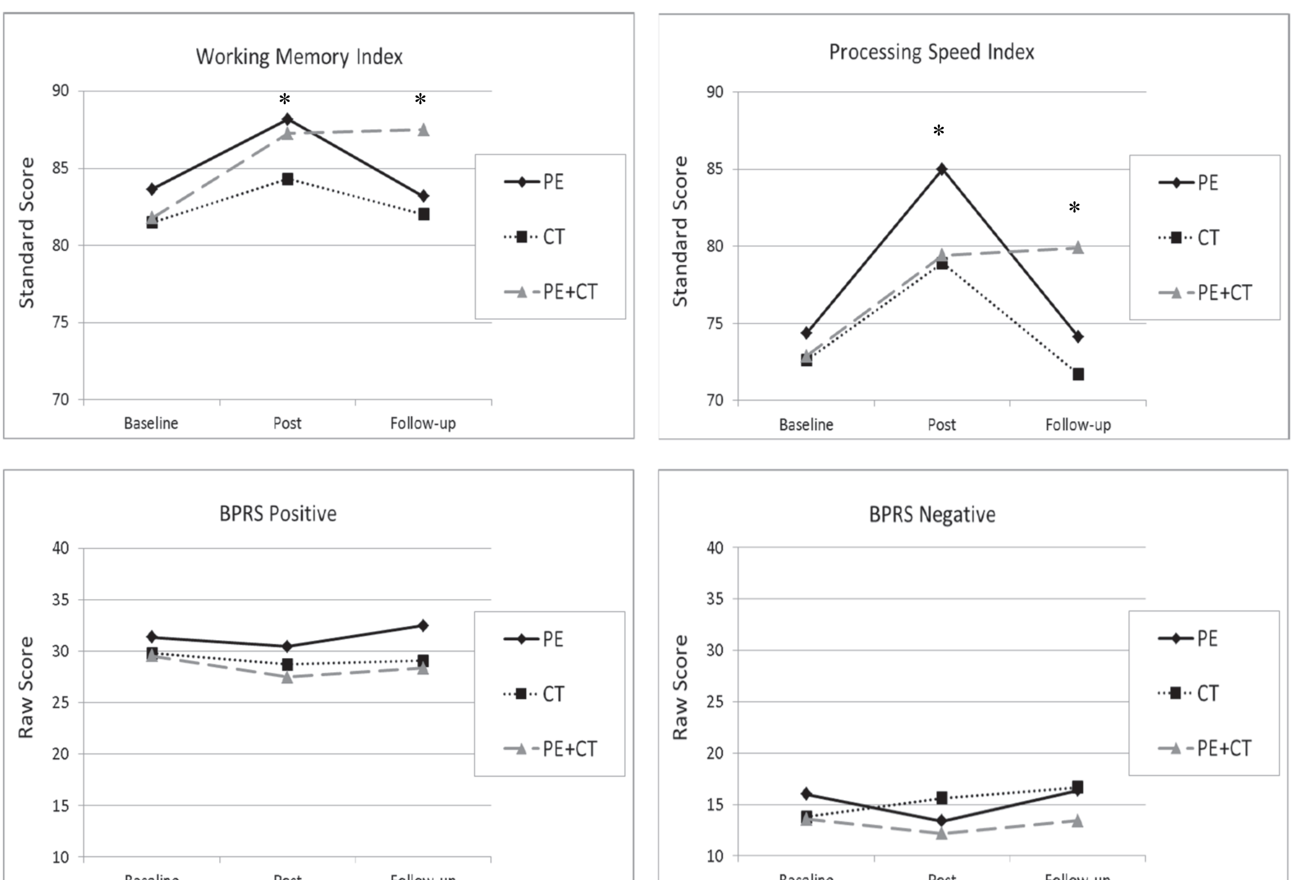

Fig. 2. Working memory and processing speed indices and symptoms at baseline, post, and follow-up (2 months).

Table 2
Point biserial correlation; relationship between high-low baseline motivation and residual changes scores from baseline to post (3 mo).

Residual change scores (Baseline to post)	PE		CT		PE + CT	
Baseline motivation	Low	High ±	Low	High	Low	High
Working memory	0.04	0.16	0.02	0.22*	0.15	0.26**
Processing speed	0.06	0.20*	−0.03	0.21*	0.22*	0.25*
BPRS negative Sx factor	0.19	−0.25**	−0.06	0.08	−0.20*	−0.22*

± Median split: Intrinsic Motivation Inventory.

Factor from baseline to post in PE and PE + CT, there were no significant differences in BPRS change scores between the groups at post or follow-up.

When participants in each of the three conditions were separated into high or low motivation at baseline (IMI median split), highly motivated participants showed greater changes on the WMI and/or PSI at post regardless of whether they were in CT alone or PE + CT (Table 2); however, participants who did PE with or without CT, showed improvement in negative symptoms at post. Notably, those who did PE + CT, *irrespective of motivation level*, showed improvement in both negative symptoms and processing speed (Table 2).

4. Discussion

This is among the first reports disentangling the individual and synergistic effects of physical exercise and cognitive training in schizophrenia. In this very first study looking at community effectiveness, PE alone improved processing speed more than CT alone; however, only the combination of PE and CT led to more enduring cognitive gains, even 2 months after interventions were discontinued. As is common in studies that examine effortful cognitive treatments, highly motivated participants benefited more in terms of cognition. However, participants who did PE and CT, *including those with low motivation*, saw improvements in negative symptoms. This was true despite no payment for attending treatment sessions, as the treatments still managed to achieve a high degree of compliance. It is also worthwhile to note that this was accomplished in loosely monitored/supervised groups. Many PE efficacy studies involve highly supervised exercise training, which is time- and cost- intensive and not applicable to real world exercise. These interventions then fail when exercise is unsupervised and effectiveness is far less than efficacy (Taylor and Pescatello, 2016).

We speculate that the self-determined exercise regimen and neurofeedback CT platform increased task motivation and helped to increase treatment compliance, thereby possibly maximizing the benefits of both interventions. In PE specifically, at the end of the study, 78% had chosen to do each activity at least once. This highlights that, given the choice, the overwhelming majority of participants preferred a varied exercise regime, with PE choices based on their personal preferences at each session. Our findings suggest a combination of these treatments, with a self-determined exercise program and a neurobiological gauge of cognitive task engagement, may offer superior, enduring treatment effects compared to a single modality.

Several factors should be considered in interpreting our findings. First, the intensive outpatient treatment days are more structured compared to usual outpatient programs, and this could have encouraged attendance. While treatment was not mandated, about a third of the participants receive Medicaid transportation services to and from the program (the rest take public transportation or walk). That being said, overall dropout in this type of intensive outpatient schizophrenia program has previously been reported to be 37% in the first month (Kurtz et al., 2015). In contrast, the current finding that 93–96% completed the entire intervention over 3 months speaks to the high level of engagement regardless of outpatient treatment format. Second, while the choice of PE from a menu of activities improved compliance to exercise, the wide range of exercises may not be feasible for other community programs. A prescribed and specific exercise regimen is more portable. Third, non-specific effects of time and/or other interventions could have played a role in the outcome. Given that this was a community program, we could not limit participant involvement in other therapies including exercising on their own at home. Four, while assessments were conducted by separate program staff than those who provided the interventions, they were not blind to treatment allocation. Finally, the third arm of PE and CT only received half a dose of PE and half a dose of CT, with the brevity of these interventions possibly impacting the findings. We are currently studying physical activity predictors relative to outcomes and varying PE and CT doses, which is what will be needed to better quantify dose response. We also intend to conduct a blinded RCT that includes comprehensive, gold standard measures of physical fitness and physical activity (VO2 max test) and neurobiological measures that will allow us to study whether the synergistic intervention of PE and CT exerts measurable effects on a putative biological mechanism of action and whether this change is related to clinical outcomes.

Conflicts of interest statement

All authors declare that they have no conflicts to disclose.

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