EFFECTS OF PHYSICAL EXERCISE ON BRAIN AND COGNITIVE FUNCTIONING

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EFFECTS OF PHYSICAL EXERCISE ON BRAIN AND COGNITIVE FUNCTIONING

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EDITORIAL
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Editorial: Effects of Physical Exercise on Brain and Cognitive Functioning

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Editorial on the Research Topic

Effects of Physical Exercise on Brain and Cognitive Functioning

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This Research Topic (RT) focused on the effects of physical activity (PA) on brain and cognitive functions across the lifespan. A growing body of literature highlights how a physically active lifestyle is associated with reduced risk of dementia, better cognitive functioning, physiological changes in the brain and overall wellbeing. In this vein, studies on people with a sedentary lifestyle highlight an increased risk of cardiovascular diseases and a higher rate of early mortality. However, many studies found contrasting or inconclusive results, depending on different targeted population, tests, and methodologies. Age and activity type seem to influence brain state, but underlying mechanisms remain unclear. This RT addresses how the brain and cognitive functioning is influenced by PA, as well as the psychological benefits of an active lifestyle across the lifespan. It contains 9 contributions on the effect of physical exercise on brain plasticity and cognitive functioning, including original research articles (5), systematic reviews and meta-analyses (3), and a brief research report (1).

How can older adults counteract age-related declines and lead longer, healthier, and fuller working lives? Across the lifespan, the brain exhibits notable plasticity and adapts to environmental changes via modifying brain function and neural connectivity (Goh and Park, 2009; Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Park, 2014). PA, cognitive training, and social engagement are major intervention approaches to improve brain health and cognitive functioning across the lifespan (Hillman et al., 2014; Ballesteros et al., 2015; Donnelly et al., 2016; Kramer and Colcombe, 2018; Ballesteros, 2022). A great deal of research supports that PA protects against age-related cognitive declines enhancing executive functions and memory (Hötting and Röder, 2013; Voelcker-Rehage and Niemann, 2013). This RT aims to provide a current picture of the state of the art on the effect of PA interventions on brain and cognition across the lifespan in healthy individuals and patients with type 2 diabetes mellitus (T2DM).

BRAIN NETWORK MODULARITY OF PA IN CHILDREN, ADOLESCENTS, COLLEGE STUDENTS, AND MIDDLE-AGED ADULTS

In their research article, Chaddock-Heymann et al. use brain network modularity as a predictor of training outcomes in 8-to 9-year-old children. In the training but not in the control group, higher modularity of brain networks at baseline was associated with greater improvements in executive functions, cognition, and mathematics. This article is the first to show how the effectiveness of PA on cognition and scholastic performance in children is dependent on baseline brain organization.

The cross-sectional study by Feraco and Meneghetti investigated the relation between years of practicing a sport and both, fluid reasoning and six soft skills. In total 1,115 individuals (10–18 years) filled in a questionnaire for assessing soft skills and completed the Cattel test to assess fluid reasoning. The results confirmed the positive effect of PA on fluid reasoning and adolescents' soft skills.

Salas-Gómez et al. investigated the association between PA with memory and executive functions in a sample of 206 college students. PA was assessed with the IPAQ-SF questionnaire. The authors found that PA correlated with several tests of executive functions, especially inhibitory control. The practice of PA improves the ability to inhibit automatic responses and to show mental flexibility.

Taking a neuroscience perspective, Do et al. used the quantitative approach for coordinate-based activation likelihood estimation (ALE) meta-analysis to find out possible differences in the neural mechanisms underlying motor decision making of experts and novices. A total of 12 studies with 219 motor experts and 210 novices were included in ALE. Greater activation was found for novices compared to experts in the bilateral occipital lobe, left posterior cerebellar lobe, and left middle temporal gyrus. The results suggest that long-term motor training leads to functional reorganization of the brain that is associated with neural efficiency in athletes.

Chou et al. examined the sustained effects of acute resistance training on inhibition in healthy middle-aged adults assigned to exercise or control groups. The resistance exercise consisted of two sets of 7 exercises. The Stroop test was administered before, after training, and 40 min post-training. The findings suggest that a moderate intensity resistance training improves executive functions.

It is well-known that sedentary behavior has negative effects for cognitive performance. Heiland et al. conducted a randomized crossover study to investigate the effects of frequent, short PA breaks, during long sitting periods on cognitive task-related activation of the prefrontal cortex. In the study, 13 middle-aged adults underwent three-3-h seated conditions in which they were interrupted every 30 min by different 3-min break activity (social interaction, walking, or simple resistance activity). Cerebral blood flow decreased in the most difficult memory task after the walking break condition. However, some aspects of working memory performance improved, suggesting a neural efficiency effect. Moreover, mood and alertness improved after walking breaks. Therefore, short walking breaks have positive effect in middle-aged adults to support performance on cognitively demanding tasks.

BRAIN AND COGNITIVE CHANGES ASSOCIATED WITH PA AND COMBINED MULTI-DOMAIN INTERVENTIONS IN HEALTHY OLDER ADULTS AND PATIENTS WITH T2DM

Polk et al. use a multimodal modeling approach for investigating the effects of aerobic training on regional gray-matter structural integrity in older adults. Results showed that 6-month at-home aerobic exercise 3–4 days a week increased cardiovascular fitness and maintained gray-matter structural integrity in brain areas showing exercise-induced volume changes. Thus, aerobic fitness interventions might contribute to brain maintenance in sedentary older adults.

Rieker et al. conducted a systematic review and multilevel meta-analysis to investigate whether combined training that includes PA and cognitive training would be more effective than single physical or single cognitive training. Fifty studies were included in the meta-analysis involving 6,164 healthy older adults and 783 effects sizes that were submitted to a three-level meta-analysis. The results revealed a small advantage of combined training on cognitive outcomes that was maintained at follow-up. Moreover, combined physical and cognitive training produced some advantage over single cognitive training in improving attention, executive functions, and processing speed. Improvements were highest when the intervention was performed in a social context even though individual training obtained similar results in balance as group training.

The prevalence of T2DM is a global health problem related to unhealthy diet and lack of exercise. T2DM patients have a high risk of developing cognitive decline characterized by long-term explicit memory and executive functions deficits (Redondo et al., 2015, 2016). Ni et al. in their systematic review and meta-analysis investigated whether exercise alone could improve cognition in 738 older patients with T2DM. The results indicated that exercise improved patient global cognition significantly and was not influenced by intervention modality, intervention duration, or cognitive impairment.

In conclusion, the studies included in this RT provide findings on different types of PA interventions as a useful way to change brain and cognitive functioning across the lifespan. Our hope is that this RT will inspire researchers to design and conduct new intervention studies aiming at improving brain health, wellbeing, and cognition at all ages.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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Physical Activity Is Associated With Better Executive Function in University Students

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Introduction: In recent years, the study of the benefits that physical exercise has on brain health has acquired special relevance. In order to implement exercise as an intervention to protect the brain, it is important to have a more clear idea of its effect in the young population. However, few studies have been carried out on these ages.

Objective: The main objective of our study was to evaluate the association between physical activity (PA) with memory and executive function, in university students, analyzing the modulatory effect of sex.

Methodology: We collected socio-demographic and life habit information, as well as data on the PA that was carried out during the previous week using the international PA questionnaire short version (IPAQ-SF) questionnaire in 206 university students (mean age 19.55 ± 2.39; 67.5% women). Memory and executive function were assessed using a comprehensive battery of validate cognitive tests. Univariate and multivariate analyses were performed to correlate PA with cognitive tests scores and to evaluate the potential synergistic role of sex.

Results: The main finding was that the total amount of PA correlated positively with several tests that evaluated aspects of executive function, specifically Stroop Colors (Pearson's $r = 0.17$; $p = 0.01$) and the Stroop Test Color–Word (Pearson's $r = 0.15$. $p = 0.03$). These results were adjusted by a large number of possible confounders and modifying variables in a multivariate analysis, like age, sex, academic record, day of the week, and time at which the test was performed. Additionally, we found out that sex had a synergistic effect with PA on the executive test Trail making test-A (TMTA), and in women, this association was stronger than in men. The more PA women reported, the better they performed, that is to say that they took less time to finalize the TMT-A (interaction term between PA and sex: $b = -0.0009$; $p = 0.014$).

Conclusion: Our study adds evidence of the benefit of PA in cognition in the young population, specifically in the executive inhibitory control, and more significantly in women.

Keywords: neuropsychological tests, physical activity, executive function, sex factors, women, young adult

INTRODUCTION

In recent years, the study of the effects of physical activity (PA) on brain health and the improvement of cognitive function has acquired special attention. This has been mainly driven by findings from several studies reporting the association between PA and active lifestyle and a decrease in dementia risk and cognitive improvement at old age (Larson et al., 2006; Wang and van Praag, 2012; Bherer et al., 2013; Prakash et al., 2015; Duzel et al., 2016; Santos-Lozano et al., 2016; Engeroff et al., 2018). It has also been considered as a potential strategy to improve academic performance, cognitive abilities, and intellectual function in children (Tomporowski et al., 2008), although the evidence for this is limited (Li et al., 2017).

There have been an increasing number of randomized clinical trials addressing the effect of PA on cognition in different age groups (Best, 2010; Liu-Ambrose et al., 2010; Nouchi et al., 2014; Iuliano et al., 2015; Álvarez-Bueno et al., 2017). Several meta-analyses supported the causality of this association, showing a low-to-moderate effect size on the improvement of cognitive aspects, especially executive function, after aerobic exercise sessions (Chang et al., 2012; Verburgh et al., 2014; Ludyga et al., 2016; de Greeff et al., 2018; Loprinzi et al., 2019) or high intensity and frequency (Wang et al., 2019).

From a basic research perspective, it has been reported that regular PA has a direct effect at the neuronal level, enhancing synapses and vascularization (Wang and van Praag, 2012; Erickson et al., 2015). Animal studies support the hypothesis that brain-derived neurotrophic factor (BDNF) would play a key role in this process (Wang and Holsinger, 2018). In the young adult, who is at a critical stage in perfecting neuronal pathways and strengthening synapses, PA may become especially important in the development of brain functions (Tomporowski et al., 2008). However, the mechanisms by which cognitive abilities improve in physically active individuals are not fully understood (Lautenschlager et al., 2008).

Although pooled analyses are consistent with an association, there are relevant discrepancies between authors, and cognitive function improvements after PA interventions are not conclusive in all trials (Colcombe and Kramer, 2003; Hillman et al., 2006; Smith et al., 2010; Gates et al., 2013; Öhman et al., 2014; Iuliano et al., 2015; Rezab, 2015; Cox et al., 2016; Ludyga et al., 2016; Barha et al., 2017). Differences may be due to issues such as the type of PA intervention, the targeted populations, the neurocognitive tests selected as main outputs, and the time period of the trial (Martín-Martínez et al., 2015; Martínez et al., 2017).

There are relevant aspects that need to be further elucidated. Most of the studies assessed PA either in the middle and later stages of adult life or in childhood–adolescence. There is currently insufficient information on the influence of PA on young adults (Guiney and Machado, 2013; Verburgh et al., 2014; Cox et al., 2016; Engeroff et al., 2018). When assessing the effect of acute PA, the benefit on cognitive functions appears to be clear in children and adolescents. However, when chronic PA is evaluated in different populations, the benefit is not yet entirely clear. In this sense, it is particularly important to carry out well-designed longitudinal studies, since today, we have a very sedentary young population, and this may influence the development of executive functions in the long term (Verburgh et al., 2014).

The cognitive pattern associated with PA is not fully established, as comprehensive assessments systematically exploring memory and executive domains are not frequently published, and many of the studies report on specific cognitive tests only.

There is some evidence that biological sex has a differential influence on the type of memory. These differences, moderated by psychological factors and physiological parameters, could be modified in response to PA (Loprinzi and Frith, 2018). Along these lines, two meta-analyses conducted in 2003 and 2017 concluded that studies that included more women tended to show greater cognitive benefits associated with PA than studies with fewer women (Colcombe and Kramer, 2003; Barha et al., 2017). A randomized, controlled clinical trial evaluating the effect of acute PA on memory found that young women performed episodic memory tasks better than men (Johnson and Loprinzi, 2019). In addition to memory, studies evaluating the effect of endurance PA showed in elderly women a clear benefit on executive functions (Liu-Ambrose et al., 2010). Although in this previous study there was no male control group, we hypothesize that PA has a positive effect on executive function cognitive functions, and this effect could be more relevant in women.

The main objective of our study was to evaluate the association between PA with memory and executive function, in university students, analyzing the modulatory effect of sex.

MATERIALS AND METHODS

Design

This is a cross sectional study to assess the association between reported PA and cognitive performance determined by a comprehensive battery of neurocognitive tests (von Elm et al., 2008).

Participants

The study included all university students enrolled in the academic year 2013–2014 at University Schools Gimbernat—Cantabria, Attached to the University of Cantabria. Exclusion criteria were a history of severe cranioencephalic trauma, neurological diseases, dyslexia, color blindness, difficulties with the Spanish language, and sensory deficits.

The study was reviewed and approved by our institutional review board (Cantabria Research Ethics Committee ref. 2012.152), and we followed the ethical principles of the Declaration of Helsinki (World Medical Association, 2020). All participants signed an informed consent before entering the study. At study baseline, all participants were over 18 years of age except for eight individuals aged 17. They were all first year students that turned 18 during the academic course. In agreement with our review board, the eight under-18 participants signed the written informed consent document during the study period once they turned 18 years.

Materials and Procedure

We interviewed all participants in two individual sessions lasting for 30 min. First, participants filled out the international PA questionnaire short version (IPAQ-SF; Rangul et al., 2008). The consumption of alcohol and other drugs, like cannabis, and sociodemographic information were also registered. In the second part, we administered to all participants a battery of neurocognitive tests validated for the study of young population and aimed at assessing memory and executive functions (Peña-Casanova et al., 2012). The assessors were given prior training in order to administer and evaluate correctly the cognitive tests in a standardized way. A logical memory test was given (WMS-III; Sueiro and Pereña, 2004; Aguirre-Acevedo et al., 2019), together with the CERAD word list (Morris et al., 1989; Mirra et al., 1991) to study episodic verbal memory; the Rey–Osterrieth complex figure test (ROCF), copy and recall (Tulsky et al., 2003) to test for constructional apraxia and differed visual memory; the digit span test WAIS-III (Sueiro and Pereña, 2004; Aguirre-Acevedo et al., 2019) to test working memory, attention span, and concentration; the standardized version of the color word test (STROOP) to check capacity to inhibit automatic response and the Trail making tests (TMT) A and B to evaluate visual–motor speed (part A) and attention and mental flexibility (part B; Golden, 2001; Golden and Freshwater, 2002).

Statistical Analysis

To quantify the PA based on the metabolic equivalents (MET), following the criteria established by the IPAQ, we proceeded by calculating the total METs corresponding to a week (Ara, 2005). Brisk walking was equal to 3.3 METs, moderate and vigorous PA to 4 and 8 METs, respectively. Thus, the quantification of the PA was done using the following formula:

$$\begin{aligned} \text{Total PA} \quad = \quad & \text{brisk walking(3.3 METs} \times \text{minutes} \\ & \times \text{amount of weekdays)} \\ & + \text{moderate PA (4 METs} \times \text{minutes} \\ & \times \text{amount of weekdays)} \\ & + \text{vigorous PA (8 METs} \times \text{minutes} \\ & \times \text{amount of weekdays).} \end{aligned}$$

Pearson's test was used to evaluate the correlation between the total METs of PA and the results of the cognitive tests. In addition, the participants were categorized according to their alcohol habits, dividing them into binge drinkers (BD) or non-binge drinkers (non-BD). A multivariant analysis was conducted through ANCOVA containing possible confounders or modifying variables of the effect, including the PA, age, sex, academic record, day of the week and time at which the test was performed, the person carrying out the examination, and whether they were or not categorized as BD. We assessed the interaction between sex and PA for each of the neuropsychological tests using ANCOVA. Additionally, the possible interaction between PA and sex was evaluated by a simple moderation analysis with the process package for SPSS (Bolin, 2014; Hayes and Little, 2018).

All statistical analyses were carried out using SPSS 19.0 (Statistical Product and Service Solutions IBM SPSS Statistics 19.0 2010).

RESULTS

The final sample included 206 individuals, with a mean age of 19.55 ± 2.39 years, of whom 67.5% were women. Only two foreign students were excluded due to their lack of understanding of the Spanish language.

The students performed on average 1.5–2 days of vigorous PA (e.g., running, swimming, or biking), with a mean of 37.5–57.9 min per day. Days per week spent on moderate PA were 1.4–1.7, employing 37.5–45.2 min per day on average. **Table 1** shows the most relevant sociodemographic characteristics and PA habits.

Table 2 and **Figure 1** depict the students' neuropsychological test results and their correlation with the total amount of METs of PA carried out weekly. A statistically significant positive correlation was found for Stroop Test Words (Pearson's $r = 0.157$; $p = 0.024$), Stroop Test Colors (Pearson's $r = 0.17$; $p = 0.01$), and the Stroop Test Color–Word (Pearson's $r = 0.15$. $p = 0.03$). That is to say, the more PA the students performed, the more items were correctly named in the three subtests.

We used ANCOVA adjusting for age, sex, academic record, BD, and other possible modifying variables such as the week of the day and the time of the day the tests were conducted. The Stroop Test Colors, and the Stroop Test Color–Word remained statistically associated to PA. TMT-A and TMT-B were borderline, which significantly correlated at the univariate analysis TMT-A (Pearson's $r = -0.13$; $p = 0.07$ and Pearson's $r = -0.12$; $p = 0.08$), which means that individuals with higher levels of PA tended to perform these tests better, that is, in fewer seconds. However, after adjustment for covariates, these results did not reach statistical significance. No other cognitive test was significantly correlated with PA.

TABLE 1 | Sociodemographic characteristics and international physical activity questionnaire (IPAQ) results.

	Total (*N* = 206)
Years of age (mean ± SD)	19.6 ± 2.4
Women (%)	67
Academic record 0/10 (mean ± SD)	6.3 ± 1.4
Days per week of vigorous activity (mean ± SD)	1.5 ± 2
Minutes per day of vigorous activity (mean ± SD)	37.5 ± 57.9
MET of vigorous activity (mean ± SD)	900.5 ± 1685.1
Days per week of moderate activity (mean ± SD)	1.4 ± 1.7
Minutes per day of moderate activity (mean ± SD)	37.5 ± 45.2
MET of moderate activity (mean ± SD)	335.2 ± 512.9
Days in which they walked >10 (mean ± SD)	5.4 ± 2.1
MET walking (mean ± SD)	811.5 ± 986.5
MET TOTAL (mean ± SD)	2,043.3 ± 2,111.3

Abbreviation: MET, metabolic equivalent.

TABLE 2 | Neuropsychological test results and their correlation with the total amount of physical activity in METs.

Neuropsychological test	Pearson's *r* correlation with total physical activity	*p*-value	*p*-value^
WMS-III Logical memory word	−0.09	0.18	0.23
ROCF copy score	0.09	0.23	0.68
ROCF delayed recall	0.10	0.17	0.33
CERAD word list memory	0.04	0.55	0.99
CERAD word list recall	0.06	0.44	0.42
Digit span forward	0.06	0.36	0.22
Digit span backward	−0.03	0.63	0.99
Stroop Test Words	**0.16***	**0.02***	0.13
Stroop Test Colors	**0.17***	**0.02***	**0.01***
Stroop Color–Word	**0.15***	**0.03***	**0.03***
WMS logical memory delayed recall	0.01	0.88	0.91
TMT-A	−0.13	0.07	0.34
TMT-B	−0.12	0.08	0.29

*Note: *p < 0.05, ^p-values were adjusted by age, sex, academic record, day of the week, time at which the test was performed, the person carrying out the examination, and binge drinking pattern. Abbreviations: TMT-A, Trail making test A; TMT-B, Trail making test B.*

Last, we evaluated the effect of PA on the neuropsychological tests measuring the executive function with regard to the sex. **Table 3** and **Figure 2** show that in the stratified analysis, there was a negative correlation with the TMT-A test, which was only statistically significant in women (Pearson's $r = -0.26$; $p = 0.01$). Therefore, the more PA women performed, the better they did the task, spending less time to accomplish it. Finally, we assessed the interaction between sex and PA for each of the neuropsychological tests using ANCOVA. TMT-A was the only one in which the interaction term sex and total PA was statistically significant ($p = 0.035$). To gain a better understanding of this interaction, we carried out a simple moderation analysis. These results are shown in **Table 4** and again reflects that in our study, sex played a significant modulating effect on the influence of PA on the executive function test TMT-A ($b = -0.0009$; $p = 0.014$).

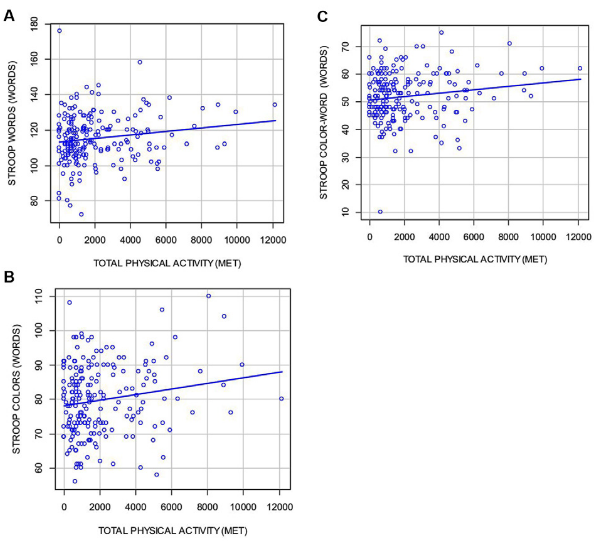

FIGURE 1 | Scatter plots showing Stroop test results (**A** = words, **B** = colors, and **C** = color-word) and their correlation with the total amount of physical activity (PA) in metabolic equivalent (METs).

TABLE 3 | Correlations between the total METs of physical activity and the neuropsychological tests stratified by sex.

Neuropsychological test	Men (*N* = 67)		Women (*N* = 139)	
	Pearson's *r*	***p*-value**	**Pearson's *r***	***p*-value^**
Stroop Test Words	0.22	0.16	0.09	0.54
Stroop Test Colors	0.27	0.06	0.11	0.40
Stroop Test Color–Word	0.25	0.08	0.09	0.60
TMT-A	0.09	0.88	**−0.26***	**0.01***
TMT-B	0.03	0.99	−0.20	0.04

*Note: *p < 0.05, ^Bonferroni-adjusted p-value.*

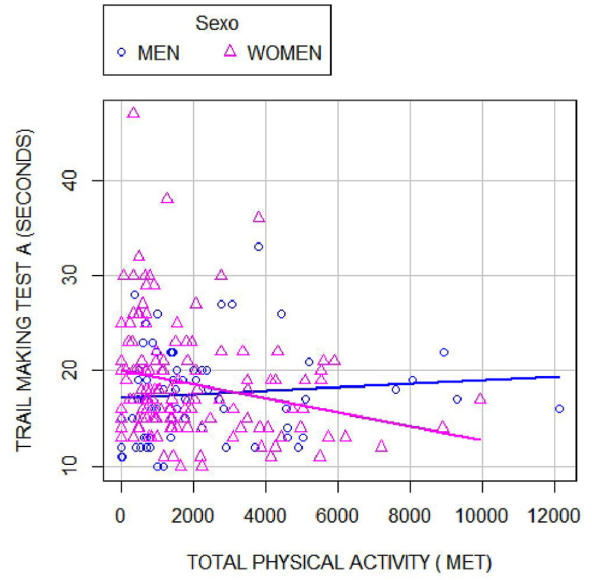

FIGURE 2 | Scatter plot showing Trail making test A results and their correlation with the total amount of METs of PA stratified by sex.

DISCUSSION

In our analysis, we observed that there was a statistically significant positive correlation between PA and all components of the Stroop test (words, colors, and color–word). After multivariate analysis, colors and color–word subtests remained significant, adjusted by the main covariates and potential confounding factors.

The Stroop test consists of three subtests: in the first one, the subject must read the words "red," "green," and "blue" printed in black ink and randomly arranged in columns; in the second subtest, he must name the color of the ink on which the symbols "XXX" are printed, arranged in columns; and on the third subtest, he must name the color of the ink on which the words "red," "green," and "blue" are printed, but not read

TABLE 4 | Moderating effect of sex on the relationship between the physical activity and TMT-A.

Dependent variable	Predictor	b	se	*t*	*p*-value
1. Interaction effect of SEX on the TMT-A					
TMT-A	Total physical activity	−0.0003	0.0002	−1.4660	0.1442
	Sex	2.9378	1.1343	2.5899	0.0103
	Total physical activity*sex	**−0.0009***	0.0004	−2.4905	**0.0136***
Sex	**Effect**	**Se**	***t***	***p*-value**	**95% CI**
2. Conditional effects of the physical activity at sex type					
Male	0.0002	0.0003	0.6908	0.4905	−0.0004; −0.0007
Women	−0.0007	0.0002	−2.9484	0.0036	−0.0012; −0.0002

*$p < 0.05$.

the word. The score of each sheet consists of the number of items read in 45 s. Stroop test evaluates key components of the executive function, chiefly the ability to inhibit stimuli that trigger automatic responses, cognitive control capacity, and mind flexibility, thus, our main finding suggests that the increased PA may improve these cognitive abilities in young adults since the more PA, the greater the number of items the participants were able to read.

Similar findings were shown in a study with preadolescents (between 7 and 12 years old; Buck et al., 2008). In this population, age was reported as a significant modulator of the effect of PA on the three Stroop tests, that is, the older the participants, the larger was the effect size of PA on interference control. Our multivariate analysis showed that age was not an effect modulator for our population; however, our volunteers were older, and their age range was narrower. A different degree of prefrontal cortex (PFC) maturation, which is related to the development of inhibitory control, between both populations might explain the diverse effects observed (Dahl, 2004). It was postulated that aerobic exercise could have a greater impact on those individuals in which the executive function is still developing (Ludyga et al., 2016). On the other hand, in an elderly population (on average 79 years), similar results were also shown by other authors who found that the amount of PA explained a small, but significant part of the variance in Stroop color scores and interference (Bixby et al., 2007).

There are a few other observational studies evaluating the effect of a physically active lifestyle on executive function. Hillman et al. (2006) reported a faster reaction time associated with PA in subjects between 15 and 71; this result was independent of age. On the other hand, a recent study, carried out in university students, of a similar age range as our population, that evaluated the relationship between PA, reported by the IPAQ (long version), and executive function, found no association (Ho et al., 2018). Despite a similar design and target population, there are several methodological differences. First, the instrument used to evaluate the executive function differed between studies. Ho et al. (2018) used the flanker task—a task related to attention and inhibition that has been shown to activate similar brain regions in functional MRI as the Stroop test, such as the anterior cingular cortex (APP) and left prefrontal cortex (lPFC; Fan et al., 2003). Despite the similarity of the two neurocognitive tests, a study reported that the time needed to resolve the response conflict in Stroop's task did not predict the time needed to resolve the response conflict in the flanker task, and therefore, the interference scores between the two tasks were not correlated. That led the authors to postulate that, although both tasks require the use of the same brain regions, the Stroop test is more demanding of frontal executive resources since this test involves a verbal output and implies a more diverse set of stimuli (Stins et al., 2005). In addition, these discordances may also be due to the different versions of the IPAQ that were used. While they opted for the long version, for our study, we chose the short version (IPAQ-SF). The IPAQ is an instrument that has been validated in a multitude of countries like Spain (Rangul et al., 2008; Román Viñas et al., 2013), and it has been widely used in diverse populations in its long as well as short version (Craig et al., 2003; Rodríguez-Muñoz et al., 2017; Rubio et al., 2017). A recent study carried out in Spanish university students aimed to validate the IPAQ-SF with an objective measurement of the PA through accelerometers, concluding that this questionnaire was a reliable tool to assess PA in the same population as our study (Rodríguez-Muñoz et al., 2017).

The second objective of this study was to assess whether sex modulates the effect of PA on cognitive functions. TMT-A was the only test in which the interaction term of sex and PA was statistically significant. TMT-A evaluates the attentional function, perceptual–motor speed capability, visual tracking skills, visoconceptual exploration, and visomotor exploration. Thus, our finding suggests that the increased PA may be related to these cognitive abilities in women.

This finding was consistently reported in the literature. In several clinical trials assessing the role of PA on mild cognitive impairment, greater benefits of aerobic training and resistance on cognition in women, specifically on executive function, were observed (van Uffelen et al., 2008; Baker et al., 2010; Nagamatsu et al., 2012). Similarly, a recent meta-analysis of clinical trials conducted in healthy volunteers, older than 45 years, also showed a greater improvement in executive function in those studies with a higher proportion of women. The largest improvement was obtained in those studies with aerobic interventions, resistance, or multimodal training performed for at least 2 months and at least once a week (Barha et al., 2017). Despite these findings, there is no clear explanation why in women, the effect of PA is greater than in men. Our study adds further evidence, reporting, as far as we know, for the first time, a statistically significant interaction term between sex and PA in a multivariate model.

No association was found with PA and any of the other neurocognitive tests carried out in our study. Functions such as episodic verbal memory, constructive apraxia, delayed visual memory, and working memory did not change significantly according to the levels of PA. There is little research on the influence of PA on these functions in young people. As a possible explanation, it has been postulated that brain at this age achieves its maximum development in areas related to these functions so that it would be difficult to obtain a further improvement of these cognitive abilities (Salthouse and Davis, 2006; Rezab, 2015). We hypothesize that the specificity of the effect of PA on executive control could be related to the fact that areas of the brain, mainly the dorsolateral prefrontal cortex (dPFC), associated with this function are still developing in this age population. These same areas are more vulnerable to toxins such as alcohol in this period of life (Gill, 2002; White and Swartzwelder, 2004; Casey and Jones, 2010; Salas-Gomez et al., 2016). In a previous publication, we described that binge drinking was associated with worse executive function in this same population, and this effect was stronger in women, which is exactly the reverse pattern of what we find with PA (Salas-Gomez et al., 2016).

The IPAQ questionnaire presents obvious limitations since it only refers to the PA carried out in the previous week. This could be problematic for a population of students, as factors like the academic calendar might influence the amount of PA performed in a given week.

Another limitation was in quantifying the amount of PA using indirect tools such as IPAQ. However, this questionnaire has been widely validated, and as mentioned above, a recent study proved its usefulness in Spanish university students (Rodríguez-Muñoz et al., 2017). On the other hand, our multivariate analysis allowed adjusting by the main covariates and potentially relevant confounders, like the day of the week and the time of the day when the assessment was performed, or the rater who performs the test. Due to our cross-sectional design, our results are potentially subject to bias. For example, reverse causality could be an alternative interpretation for our data. It has been reported that professional cyclists have a higher inhibitory control than amateurs and performed significantly better in the Stroop test, leading the authors to hypothesize that their superior ability would allow them to cope with higher levels of mental fatigue and, thus, become elite athletes (Martin et al., 2016). Causality between PA and improved executive function has been consistently tested in prospective clinical trials, so we consider this explanation unlikely.

CONCLUSION

In conclusion, our study adds further evidence for the beneficial relationship between an indirect measurement of PA, through the internationally validated IPAQ-SF questionnaire, and cognition in young adults. Specifically, our findings suggest that the practice of PA might improve aspects of executive function such as the ability to inhibit stimuli that trigger automatic responses, cognitive control ability, and mental flexibility in university students. In addition, we found a synergistic effect between PA and sex, with a more intense association with females regarding attention function and perceptual–motor speed capacity.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Cantabria Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PS-J participated in the design of the study and the funding acquisition. He contributed to the formal analysis and methodology. He also participated in project administration, supervision, writing, review, and editing. DS-G participated in data curation, informal analysis, and in the investigation. She also contributed to the methodology, writing, and the original draft. MF-G participated in data curation and in the investigation. He also contributed to the methodology, writing, and the original draft. AP, ID-C, ML, and CP contributed to the investigation. All authors read and approved the final version of the manuscript, and agreed with the order of presentation of the authors.

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Brain Network Modularity Predicts Improvements in Cognitive and Scholastic Performance in Children Involved in a Physical Activity Intervention

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Introduction: Brain network modularity is a principle that quantifies the degree to which functional brain networks are divided into subnetworks. Higher modularity reflects a greater number of within-module connections and fewer connections between modules, and a highly modular brain is often interpreted as a brain that contains highly specialized brain networks with less integration between networks. Recent work in younger and older adults has demonstrated that individual differences in brain network modularity at baseline can predict improvements in performance after cognitive and physical interventions. The use of brain network modularity as a predictor of training outcomes has not yet been examined in children.

Method: In the present study, we examined the relationship between baseline brain network modularity and changes (post-intervention performance minus pre-intervention performance) in cognitive and academic performance in 8- to 9-year-old children who participated in an after-school physical activity intervention for 9 months ($N = 78$) as well as in children in a wait-list control group ($N = 72$).

Results: In children involved in the after-school physical activity intervention, higher modularity of brain networks at baseline predicted greater improvements in cognitive performance for tasks of executive function, cognitive efficiency, and mathematics achievement. There were no associations between baseline brain network modularity and performance changes in the wait-list control group.

Discussion: Our study has implications for biomarkers of cognitive plasticity in children. Understanding predictors of cognitive performance and academic progress during child development may facilitate the effectiveness of interventions aimed to improve cognitive and brain health.

Keywords: academic achievement, brain networks, brain network modularity, children, cognition, physical activity, scholastic performance

INTRODUCTION

Cognitive processes such as executive functions (inhibition, working memory, mental flexibility), attention, and memory are known to play a role in successful goal-directed behavior and scholastic performance (St. Clair-Thompson and Gathercole, 2006; Bull et al., 2008). School performance can predict success in later years (Kuncel et al., 2004; Kuncel and Hezlett, 2007), and academic placement, and educational program effectiveness, and school funding are often determined by children's performance on standardized academic tests. Thus, it is important to determine biomarkers and correlates of academic progress as well as lifestyle factors that positively influence cognitive function and scholastic performance.

Scientists have developed interventions aimed to improve executive function and scholastic performance during childhood and across the lifespan. As the brain develops structurally and functionally during childhood, this period of neurodevelopment may be particularly sensitive to lifestyle factors and intervention. For example, participation in physical activity is a promising intervention to improve cognitive and brain health during childhood and across the lifespan (Hillman et al., 2014; Donnelly et al., 2016; Kramer and Colcombe, 2018; Chaddock-Heyman et al., 2019). In particular, participation in physical activity and higher levels of aerobic fitness is positively related to cognitive function, scholastic performance, and brain health in preadolescent children (for a review see Chaddock-Heyman et al., 2014). Physically active and higher fit children outperform less active and lower fit children on cognitive and scholastic tasks, and the performance differences are paralleled by differences in brain structure and brain function (for reviews see Chaddock-Heyman et al., 2014; Donnelly et al., 2016).

Recently, scientists have begun to examine whether baseline (pre-intervention) brain properties, such as properties of brain networks, can predict improvements in performance with physical and cognitive training interventions. Brain networks are said to exhibit a modular organization, such that they are comprised of modules or sub-networks. The brain can be segregated into network modules based on connectivity patterns among individual brain regions, or nodes. Network modules reflect groupings of nodes that share high connectivity among each other. Using a mathematical approach called graph theory, a modularity metric is calculated based on the degree of within-module connections compared to between-network connections (Newman and Girvan, 2004). Higher modularity reflects a greater number of within-module connections and fewer connections between modules. A highly modular brain can be interpreted as a brain that contains highly specialized brain networks with less integration between networks.

Individual differences in baseline brain network modularity, measured during a resting-state functional MRI scan, have been found to predict improvements (i.e., changes) in performance after cognitive and physical interventions (Arnemann et al., 2015; Gallen et al., 2016; Baniqued et al., 2018, 2019; for review see Gallen and D'Esposito, 2019). In one study (Gallen et al., 2016), healthy older adults with more modular brain networks at baseline showed greater improvements on tasks involving the synthesis of complex information after cognitive training, with no predictive power of modularity in a control group (Gallen et al., 2016). In addition, in young adults involved in cognitive training with casual video games that engaged reasoning and working memory processes, baseline network modularity was positively associated with training-related improvements on untrained tasks, with no associations in participants who did not show training gains (Baniqued et al., 2019). Similarly, in patients with traumatic brain injury (TBI), higher brain network modularity at baseline was associated with greater improvements on tasks of executive function after goal-oriented attention and self-regulation training (Arnemann et al., 2015). Finally, Baniqued et al. (2018) examined whether baseline brain network modularity predicted cognitive improvements after a physical activity intervention in healthy older adults. In older adults who showed gains in aerobic fitness and cognitive function, higher brain modularity at baseline predicted greater gains in executive function from pre-intervention to post-intervention (Baniqued et al., 2018). Together, these studies suggest that brain modularity may hold predictable power across populations and interventions aimed at enhancing cognition. In the four studies in older adults, younger adults, and TBI patients, individuals with a more modular brain network organization before training were more likely to benefit from cognitive or physical intervention.

To our knowledge, the use of brain network modularity as a predictor of training outcomes has not yet been examined in children. In the present study, we examined the relationship between baseline (pre-intervention) brain network modularity and changes (post-intervention minus pre-intervention) in cognitive and academic performance in 8- to 9-year-old children who participated in an after-school physical activity intervention for 9 months compared to children randomized to a wait-list control group. We hypothesized that children in the physical activity intervention with higher baseline modularity would show greater gains in cognitive and scholastic performance compared to those with lower modularity. That is, children in the intervention may be able to better capitalize on higher levels of brain modularity to derive greater benefit from physical activity intervention. We did not have any specific predictions about baseline brain network modularity and performance changes in the wait-list control group.

MATERIALS AND METHODS

Children were recruited from schools in East-Central Illinois. Eligible participants were required to: (1) be 7- to 9-years-old; (2) have an absence of school-related learning disabilities (i.e., individual education plan related to learning), adverse health conditions, physical incapacities, or neurological disorders; (3) qualify as prepubescent (Tanner pubertal timing score; Taylor et al., 2001); (4) report no use of medications that influence central nervous system function; (5) demonstrate right-handedness as measured by the Edinburgh Handedness Questionnaire (Oldfield, 1971); (6) complete a mock MRI session to screen for claustrophobia in an MRI machine; and (7) sign an informed assent approved by the Institutional Review Board of the University of Illinois at Urbana-Champaign. A legal guardian also provided written informed consent following the Institutional Review Board of the University of Illinois at Urbana-Champaign. The guardian was asked to provide information regarding participants' socioeconomic status (SES), as determined by: (1) participation in the free or reduced-price lunch program at school; (2) the highest level of education obtained by the mother and father; and (3) number of parents who worked full-time (Birnbaum et al., 2002). Participants also completed the Woodcock–Johnson III paper-and-pencil test to assess intelligence quotient (IQ) and cognitive function (Woodcock, 1997).

The Institutional Review Board of the University of Illinois at Urbana-Champaign approved the present study. MRI scans were obtained at the Biomedical Imaging Center of the Beckman Institute of the University of Illinois, both pre-intervention and post-intervention (The post-intervention scans are not included in the present study). Children completed the cognitive tasks and scholastic performance assessment on a separate day, both pre-intervention and post-intervention, and testing occurred in a quiet, sound-attenuated room in a one-on-one setting. Children were compensated $15/h for MRI testing and $10/h for the neuropsychological testing.

Please see **Figure 1** for an illustration of the study design. Five hundred ninety children were assessed for eligibility for the FITKids2 study, and 198 were excluded due to no response (N = 37), loss of interest (N = 43), or failure of the inclusion criteria (N = 118). Three hundred ninety-two children passed prescreening, 92 children declined participation and 28 children had incomplete baseline data for primary outcomes. Two-hundred and seventy-two children were randomized into the FITKids2 physical activity intervention, and 188 children completed the resting state MRI scan at baseline (pre-intervention). Twenty-eight children were excluded following quality control checks of functional scans. Functional scans were excluded if more than 20% of volumes exhibited framewise displacement (FD) above 0.2 mm or if mean relative motion was greater than 0.5 mm. Cognitive and modularity measures greater than or less than three standard deviations from the mean were also excluded (N = 2 outlier exclusions for baseline brain network modularity, N = 1 for Cognitive Efficiency, N = 2 for Thinking Ability, N = 3 for Verbal Ability, N = 1 for Reading; results remain the same when outlier data points were included in the sample).

The present study included a total of 150 children–78 children in the physical activity intervention (45 girls and 33 boys, mean age = 8.7 years, age range 7.8–9.9 years, grades 2–4) and 72 children in the wait-list control group (37 girls and 34 boys, mean age = 8.6 years, age range 7.9–9.9 years, grades 2–4). See **Table 1** for participant information.

Woodcock–Johnson Battery of Cognitive Tasks

Children completed subtests from the Woodcock–Johnson III Tests of Cognitive Abilities (WJ III; Woodcock, 1997). Individual cognitive tests were administered to participants, and combinations of the individual tests form clusters that represent general categories of broad cognitive abilities. The cognitive performance clusters include Executive Processes, Thinking Ability, Cognitive Efficiency, and Verbal Ability.

The cognitive cluster of Executive Processes includes tasks of cognitive flexibility and rule switching (Concept Formation), sequential reasoning and spatial scanning (Planning), and attention and interference control (Pair Cancelation). During the Concept Formation task, participants were asked to identify rules and concepts that created geometric shapes. The Concept Formation task provides a measure of cognitive flexibility, rule application, and rule switching. During the Planning task, participants were asked to trace unique shapes without retracing or picking up the pencil. The Planning task provides a measure of sequential reasoning, spatial scanning, and speed in visually surveying a spatial field. During the Pair Cancellation task, participants were asked to circle two target shapes when the shapes appeared in a sequence (for 3 min). The Pair Cancellation task measures attention, concentration, and interference control.

The cognitive cluster of Thinking Ability represents fluid reasoning, visual-spatial thinking, and processing of non-language information *via* short term memory (*via* performance on tasks of Visual Auditory Learning, Spatial Relations, Sound Blending, and Concept Formation). During the Visual Auditory Learning task, participants were orally presented words that were associated with visual symbols and then asked to translate the visual symbols. The Visual Auditory Learning task measures recall of verbal labels for visual symbols. During the Spatial Relations task, participants were asked to rotate a shape *via* imagination and/or select the components of shape. The Spatial Relations task measures the ability to visualize and adjust spatial shapes and forms. During the Sound Blending task, participants were asked to name a complete word after listening to the individual syllables and phonemes that form the word, thereby providing a measure of phonetic coding. The Thinking Ability cluster also includes task performance on the task of Concept Formation.

The cognitive cluster of Cognitive Efficiency represents perceptual speed, short term memory, and the ability to store and recode information (*via* performance on tasks of

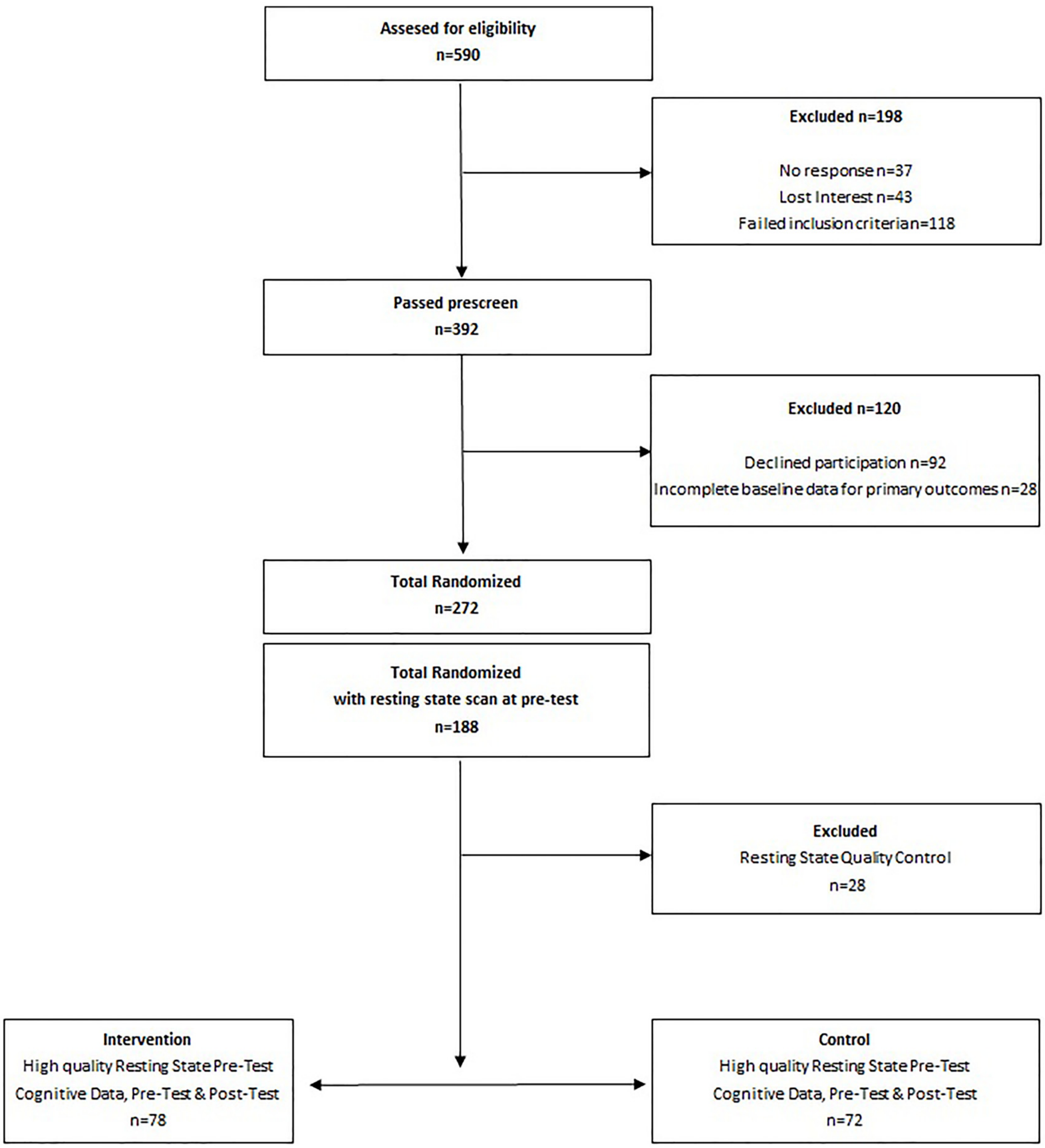

FIGURE 1 | Study design.

Visual Matching and Numbers Reversing). During the Visual Matching task, participants must quickly find and circle two identical numbers in a row of six numbers in 3 min, thereby providing a measure of perceptual speed. During the Numbers Reversed task, participants were asked to repeat a span of random numbers in reverse order, thus providing a measure of the ability to temporarily store and recode orally presented information.

The cognitive cluster of Verbal Ability is reflected by performance on a task of Verbal Comprehension, which consists of picture vocabulary, synonyms, antonyms, and verbal analogies.

Scholastic Performance

The scholastic performance was assessed with subtests from the Kaufman Test of Educational Achievement, Second Edition (Kaufman and Kaufman, 2004). Standardized scores (Mean = 100, *SD* = 15) for reading (word recognition and reading comprehension) and mathematics (math concepts and applications and math computation) were determined. Kaufman Test of Educational Achievement, Second Edition subtests have very high internal consistencies, inter-rater reliabilities, and internal validity ($r = 0.91–0.97$).

Reading achievement was determined by performance on tasks of word recognition and reading comprehension.

Specifically, the word recognition subtest involved pronouncing words of gradually increasing difficulty. The reading comprehension subtest involved reading words and pointing to the corresponding picture, acting out the action of words, and answering questions about reading passages.

Mathematics achievement was determined by performance on tasks of math concepts, math applications, and math computation. The math concepts and application subtest consisted of basic math concepts such as comparing numbers and rounding numbers, as well as problems requiring algebra, calculus, and trigonometry (88 items). The math computation subtest was a paper-and-pencil test involving the addition, subtraction, multiplication, and division of whole numbers and fractions (72 items).

Aerobic Fitness Testing

Children completed a VO_{2max} test to assess aerobic fitness. The aerobic fitness of each child was measured as maximal oxygen consumption (VO_{2max}) during a graded exercise test (GXT). The GXT employed a modified Balke Protocol and was administered on a LifeFitness 92T motor-driven treadmill (LifeFitness, Schiller Park, IL, USA) with expired gases analyzed using a TrueOne2400 Metabolic Measurement System (ParvoMedics, Sandy, Utah). Children walked and/or ran on a treadmill at a constant speed with increasing grade increments of 2.5% every 2 min until volitional exhaustion occurred.

Oxygen consumption was measured using a computerized indirect calorimetry system (ParvoMedics True Max 2400) with averages for VO_2 and respiratory exchange ratio (RER) assessed every 20 s. A polar heart rate (HR) monitor (Polar WearLink + 31; Polar Electro, Finland) was used to measure HR throughout the test, and ratings of perceived exertion (RPE) were assessed every 2 min using the children's OMNI scale (Utter et al., 2002). Maximal oxygen consumption was expressed in ml/kg/min and $VO_{2\ max}$ was based upon maximal effort as evidenced by: (1) a plateau in oxygen consumption corresponding to an increase of less than 2 ml/kg/min despite an increase in workload; (2) a peak HR $\geq$185 beats per minute (American College of Sports Medicine, 2006) and an HR plateau (Freedson and Goodman, 1993); (3) RER $\geq$1.0 (Bar-Or, 1983); and/or (4) a score on the children's OMNI RPE scale $\geq$8 (Utter et al., 2002).

Physical Activity Training Intervention and Wait List Control Group

The physical activity intervention occurred for 2 h after each school day from September until May for 150 days of the 170-day school year. The program, Fitness Improves Thinking in Kids 2 (FITKids2; NICHD grant HD069381, www.clinicaltrials.gov, Identifier: NCT01619826) was based on the Child and Adolescent Trial for Cardiovascular Health (CATCH) curriculum (McKenzie et al., 1994) and aimed at improving aerobic fitness through engagement in a variety of developmentally appropriate physical activities. The environment was non-competitive and integrated activities such as fitness activities, motor skill practice, and organized games similar to tag (Castelli et al., 2011).

Within a daily lesson, children participated in moderate to vigorous physical activity (recorded by E600 Polar HR monitors; Polar Electro, Finland, and Accusplit Eagle 170 pedometers, San Jose, CA, USA) for 30–35 sustained minutes and then intermittently up to 90 min, thus exceeding the national physical activity guideline of 60+ minutes of moderate to vigorous physical activity per day (Centers for Disease Control and Prevention, 2012; U.S. Department of Health and Human Services, 2018). Overall, children spent ∼50% of the time during the intervention engaged in moderate to vigorous physical activity (i.e., >70% of HR max, based on pre-test maximal HR from an incremental exercise test).

Each lesson began with the children completing stations that focused on a specific health-related fitness component (e.g., cardiorespiratory endurance, muscular strength). The activities were aerobically demanding and designed to encourage children to improve on previous performances by gradually increasing the number of repetitions or amount of resistance at a station. Although the stations were organized by health-related fitness components, each activity also required a motor or manipulative skill (e.g., dribbling a basketball around cones for 30-s, performing a sit-up, throwing a ball overhead). After the sustained participation and active rest rotations, the children consumed a healthy snack and were introduced to a themed educational component related to health promotion (e.g., goal setting, self-management). Each lesson concluded with the children participating in non-elimination, small group games, and activities such as dance or sports activities with modified rules selected from the CATCH curriculum. On the weekends, the children were encouraged to continue their participation in physical activity with their families, and physical activity worksheets were utilized during school holidays to log continued engagement. Average attendance across the 9-month intervention was 83.2% (*SD* = 14.12%).

The wait-list control group completed all facets of the baseline and post-intervention similar to those children who were randomized into the after-school physical activity program. As an incentive to stay in the study, children in the wait-list control group were allowed to participate in the physical activity program during the following school year (without involvement in any testing).

NEUROIMAGING METHODS

Imaging Data Acquisition

T2*-weighted resting state images were acquired with a fast echo-planar imaging (EPI) sequence with blood-oxygen-level-dependent (BOLD) contrast [TA (acquisition time) = 4 min 6 s, TR = 2 s, TE = 25 ms, flip angle = 90°, 36 3.0 mm-thick slices acquired in ascending order, Grappa acceleration factor = 2, 92 × 92 matrix resolution, voxel size 2.6 × 2.6 × 3.0]. Participants were asked to lay still with eyes closed during the resting state scan.

To assist with registration, high-resolution structural MR scans were acquired using a 3D MPRAGE (Magnetization Prepared Rapid Gradient Echo) T1-weighted sequence with

0.9 mm isotropic resolution [TR = 1,900 ms; TE = 2.32 ms; TI = 900 ms (repetition/echo/inversion times)]. All images were collected on a Siemens Magnetom Trio 3T whole-body MRI scanner with a 12-channel receiver head coil (Siemens Medical Solutions; Erlangen, Germany).

Imaging Data Analysis

Preprocessing

All imaging processing and analyses were carried out with a script library containing tools from FSL 5.0.4 (Functional Magnetic Resonance Imaging of the Brain's Software Library[1]), AFNI[2], FreeSurfer[3], and MATLAB (The MathWorks, Natick, MA, USA; Voss et al., 2016; Weng et al., 2017).

For the resting-state fMRI data, a six-degree-of-freedom rigid-body head motion correction was applied to the fMRI data *via* AFNI's 3dvolreg function, which produced six parameters of head motion (root-mean-squares of translational and rotational movement: X, Y, Z, pitch, roll, and yaw directions) for subsequent regression of spurious variance. Non-brain tissue was removed using BET, and spatially smoothing using a 6.0 mm three-dimensional Gaussian kernel of full-width at half-maximum was applied.

Then, after normalizing each global 4D dataset by the median intensity, we used an ICA-based method for further cleaning of motion-related artifacts (ICA-AROMA; Pruim et al., 2015). For baseline (pre-intervention) scans, ICA-AROMA yielded 28.5 $\pm$ 4.8 total independent components from the data, and it classified 16.7 $\pm$ 5.0 components as motion-related artifacts which were regressed out of the data (58.1 $\pm$ 12.8% of total components). ICA-AROMA removes motion-related variance from the BOLD data, and denoised volumes retain data from all time points.

Next, the denoised data were temporally filtered using AFNI's 3dBandpass to ensure that the fMRI data fell within the frequency band of $0.008 < f < 0.08$ Hz. This helps reduce unwanted noise such as high-frequency physiological signals (e.g., cardiac pulse) and low-frequency scanner drift. The frequency band was chosen to best represent the spontaneous, low-frequency fluctuation of the BOLD fMRI signal in the brain (Leopold et al., 2003; Salvador et al., 2005).

Following temporal filtering, the mean time series was extracted from three sources of non- neuronal variance: white matter signal from a region in white matter structure, the cerebrospinal fluid signal from a region in the lateral ventricle, and the global signal derived from a whole-brain mask. These nuisance signals were used as covariates to control for artifacts in the brain that may confound functional connectivity outcomes. With these three nuisance signals, the six head motion parameters obtained from the rigid body motion correction were band-passed with the same temporal filter applied to the fMRI data and included as nuisance regressors (Hallquist et al., 2013). Together, the nine band-passed nuisance regressors (white matter, CSF, global, and motion parameters) were entered into a multiple regression as independent variables predicting the resting-state fMRI data as a dependent variable using FSL's FEAT tool.

Individual EPIs were registered to high-resolution structural T1 space using the boundary-based registration (BBR) algorithm (Greve and Fischl, 2009). First, high-resolution structural images were skull-stripped using FSL's Brain Extraction Technique (BET) algorithm (Smith, 2002). Each skull-stripped anatomical image was visually inspected for errors. Then, registration of the EPIs from individual high-resolution structural space to standard MNI space was accomplished by FNIRT nonlinear registration with the default 10 mm warp resolution (Andersson et al., 2007a,b). The two resulting transformations were concatenated and then applied to the original functional image to create a functional image in standard MNI space; a reverse transform was used to register the seeds from standard MNI space to each participant's native functional space.

Network Modularity Analysis

Our primary aim was to characterize modularity, a brain network measure that compares the number of connections within modules to the number of connections between modules. Modules were identified in a data-driven fashion using Newman's spectral community detection (Newman, 2006). This approach identifies the optimal modular partition for each subject at each connection threshold.

For each participant, the preprocessed resting-state fMRI data was parcellated into 400 ROIs based on the Schaefer 2018 atlas (Schaefer et al., 2018). Then a 400 $\times$ 400 correlation matrix was generated by correlating the time-series between every possible pair of ROIs using Pearson's coefficient and applying a Fisher z-transformation. Following previous reports, the resulting correlation matrices were thresholded and binarized over a range of connection density thresholds (2–10% at 2% increments; Power et al., 2011, 2012; Gallen et al., 2016; Baniqued et al., 2018, 2019). Modularity was calculated from unweighted and undirected brain graphs using the *modularity_und* tool from the Brain Connectivity Toolbox[4]. The middle 6% threshold was used for our primary analyses, and we verified the effects at the other thresholds.

Statistical Analysis

A 2 (Group: intervention, wait-list) $\times$ 2 (Time: baseline, post-intervention) repeated measures analysis of variance (ANOVA) was conducted to explore the effect of time and the physical activity intervention on each cognitive outcome and aerobic fitness. Separate repeated-measures ANOVAs was conducted for each cognitive outcome. The repeated measures ANOVAs were conducted to confirm that cognitive performance improved from pre-intervention to post-intervention in our child sample, and to test whether the physical activity intervention had a greater effect on cognitive performance and aerobic fitness compared to the wait-list control group (a group of typically developing children over 9 months). Nevertheless, the main focus of the manuscript was to understand whether brain network

[1]http://www.fmrib.ox.ac.uk/fsl
[2]http://afni.nimh.nih.gov/afni
[3]http://surfer.nmr.mgh.harvard.edu
[4]https://sites.google.com/site/bctnet/measures

modularity at baseline predicted intervention-related changes (improvements) in cognitive and scholastic performance.

Given our hypotheses, linear regressions were employed to test associations between brain modularity at baseline (pre-intervention) and change in cognitive performance and scholastic performance. Separate regressions were performed for children assigned to the physical activity intervention group and children assigned to the wait-list control group. Cognitive performance change scores were computed as the difference in post-intervention and pre-intervention (or baseline) scores for each participant. T-scores and standardized betas (β) are presented. The alpha level for all tests was set at $p < 0.05$. 95% confidence intervals (CI) were reported.

RESULTS

Brain network modularity at baseline was not significantly associated with age ($r = -0.007$, $p = 0.93$), sex ($r = 0.004$, $p = 0.959$), SES ($r = 0.022$, $p = 0.79$), IQ ($r = -0.001$, $p = 0.991$), pubertal timing ($r = 0.027$, $p = 0.745$), aerobic fitness (VO_{2max}; $r = 0.008$, $p = 0.922$), or baseline performance for any cognitive outcomes (all $p > 0.17$).

Changes in Aerobic Fitness, Cognitive Performance, and Scholastic Performance Across Time and Intervention

To begin, we explored the effects of time and the physical activity intervention on aerobic fitness and cognitive outcomes. There was no main effect of Time ($p = 0.848$) or Group × Time interaction ($p = 0.961$) for aerobic fitness.

There was a main effect of Time for the cognitive outcomes, with children in the physical activity group and wait-list control group showing improvements in cognitive and scholastic performance from pre-intervention (baseline) to post-intervention, as predicted (except for reading achievement; **Table 1**; Main effects of Time: Executive Processes: $F = 36.441$, $p < 0.001$; Cognitive Efficiency: $F = 23.764$, $p < 0.001$; Thinking Ability: $F = 35.564$, $p < 0.001$; Verbal Ability: $F = 7.595$, $p = 0.007$; Mathematics: $F = 9.022$, $p = 0.003$; Reading: $F = 2.566$, $p = 0.111$).

The Group (physical activity intervention, wait-list control) × Time (baseline, post-intervention) interaction did not reach significance for any of the cognitive outcomes, which suggests that the physical activity group did not show significantly greater gains in performance than the control group (Group × Time interactions: Executive Processes: $F = 0.811$, $p = 0.369$; Cognitive Efficiency: $F = 1.969$, $p = 0.163$; Thinking Ability: $F = 0.319$, $p = 0.573$; Verbal Ability: $F = 1.340$, $p = 0.249$; Mathematics: $F = 0.136$, $p = 0.712$; Reading: $F = 2.211$, $p = 0.139$).

Because of our *a priori* hypotheses predicting associations between baseline brain network modularity and gains in cognitive performance with an intervention, we explored associations between baseline brain network modularity and cognitive progress (change) by group.

Baseline Modularity and Change in Cognitive Performance Clusters *via* Woodcock–Johnson

In children involved in the 9-month after-school physical activity intervention, higher brain network modularity at baseline was positively associated with a change in Executive Processes ($\beta = 0.260$, $t = 2.328$, $p = 0.023$, $N = 77$; CI: 0.0374366, 0.4817229; **Figure 2**).

In addition, in children in the physical activity group, higher brain network modularity at baseline was positively associated with a change in Cognitive Efficiency ($\beta = 0.390$, $t = 3.647$, $p < 0.001$, $N = 76$, CI: 0.1770542, 0.6035671; **Figure 3**). There were no significant associations between baseline modularity and change in Thinking Ability ($\beta = 0.134$, $t = 1.160$, $p = 0.250$, $N = 76$, CI: −0.09592174, 0.3631804) or change in Verbal Ability ($\beta = -0.019$, $t = -0.161$, $p = 0.873$, $N = 76$, CI: −0.2502647, 0.2129114).

Brain network modularity at pre-test did not positively predict cognitive performance changes in children in the wait-list control group (Executive Processes: $\beta = 0.062$, $t = 0.520$,

TABLE 1 | Mean (SD) for physical activity and waitlist control groups at baseline (pre-intervention) and post-intervention.

	Physical activity		Control	
	Baseline	Post	Baseline	Post
Age (years)	8.7 (0.5)	–	8.6 (0.5)	–
Gender	45 girls, 33 boys	–	37 girls, 34 boys	–
IQ (General)	109.2 (15.4)	–	110.9 (13.0)	–
Pubertal timing	1.4 (0.5)	–	1.3 (0.4)	–
SES	1.9(0.8)	–	1.9 (0.7)	–
VO_{2max} (ml/kg/min)	42.4 (7.3)	42.5 (7.3)	43.0 (7.1)	43.0 (6.4)
VO_{2max} percentile	35.8 (30.2)	35.5 (29.6)	38.0 (30.4)	37.5 (28.9)
Reading achievement	110.5 (13.9)	110.6 (14.0)	113.1 (14.4)	115.5 (16.0)
Mathematics achievement*	108.3 (16.2)	110.6 (17.9)	111.1 (16.2)	114.0 (17.0)
Executive processes (WJ)*	107.0 (10.4)	111.6 (9.8)	109.7 (9.8)	113.1 (9.9)
Thinking ability (WJ)	113.9 (12.9)	119.2 (12.4)	115.7(12.8)	120.0 (13.6)
Cognitive efficiency (WJ)*	98.8 (16.7)	102.3 (17.8)	98.9 (15.5)	105.2 (16.1)
Verbal ability (WJ)	107.9 (12.4)	109.1 (12.6)	109.3 (11.5)	112.1 (11.5)
Modularity (6%)	0.488 (0.062)	–	0.474 (0.065)	–

*Note: Woodcock–Johnson III paper and pencil tasks (Woodcock, 1997); SES—Socioeconomic Status (Low: < 2; Moderate: 2–3; High, >3). *p < 0.05. Association between baseline network modularity and change in performance in children involved in the physical activity intervention (uncorrected).*

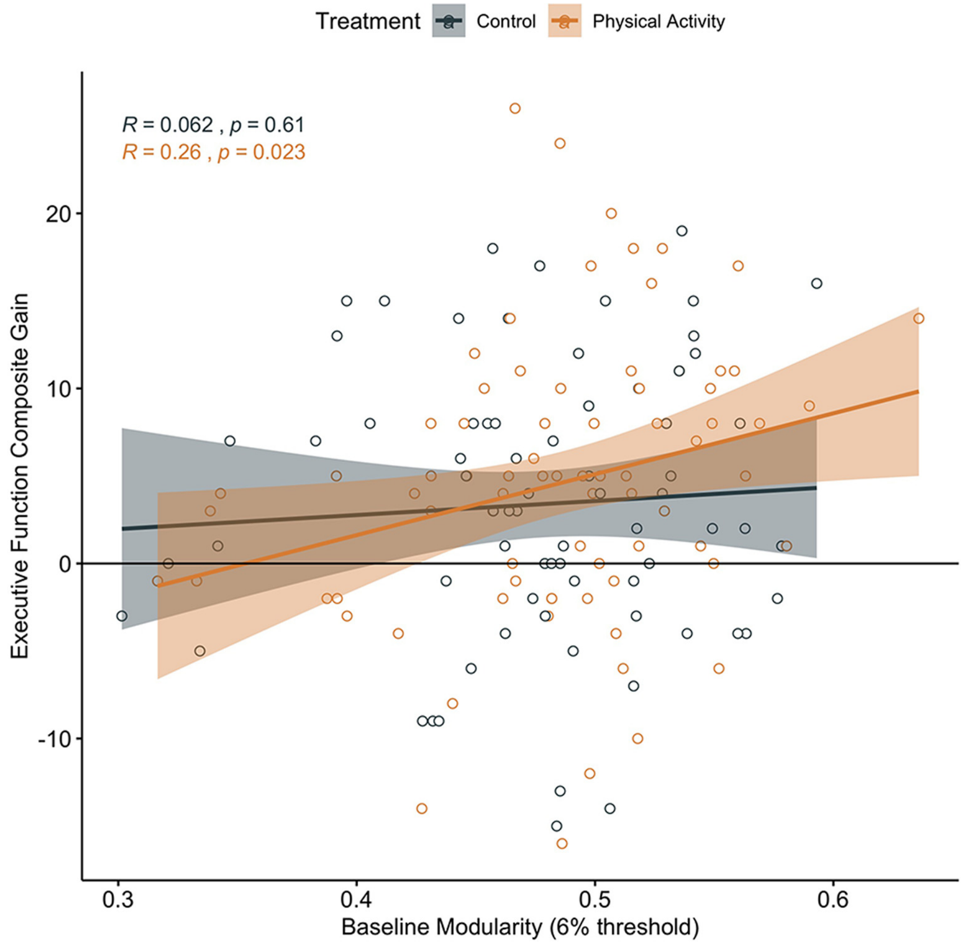

FIGURE 2 | Association between baseline brain network modularity and change in executive function by group. Significant association in children involved in the physical activity intervention (uncorrected).

$p = 0.605$, $N = 71$, CI: −0.1772713, 0.3021183; **Figure 2**; Cognitive Efficiency: $\beta = -0.319$, $t = -2.794$, $p = 0.007$, $N = 71$, CI: −0.5464083, −0.09114016; **Figure 3**; Thinking Ability: $\beta = 0.066$, $t = 0.548$, $p = 0.585$, $N = 70$, CI: −0.1750920, 0.3078135; Verbal Ability: $\beta = 0.081$, $t = 0.672$, $p = 0.504$, $N = 71$, CI: −0.1587927, 0.3199714). For Cognitive Efficiency in the wait-list control group, the effect was in the opposite direction than expected; that is, baseline brain network modularity negatively predicted change in performance, despite gains in performance from pre-intervention to post-intervention in the control group (**Figure 3**). Thus, this result was not in a meaningful direction for interpretation.

Baseline Modularity and Change in Scholastic Performance

In children involved in the physical activity intervention, higher brain network modularity at baseline was positively associated with a change in mathematics achievement ($\beta = 0.347$, $t = 3.221$, $p = 0.002$; $N = 78$; CI: 0.1323028, 0.5609004; **Figure 4**). There was no significant association between baseline brain modularity and change in reading achievement ($\beta = 0.001$, $t = 0.009$, $p = 0.993$, $N = 77$, CI: −0.2290192, 0.2310368).

Brain network modularity at pre-test did not predict scholastic performance changes in children in the wait-list control group (Mathematics: $\beta = 0.023$, $t = 0.193$, $p = 0.848$, $N = 72$, CI: −0.2366569, 0.2366569; **Figure 4**; Reading $\beta = 0.074$, $t = 0.618$, $p = 0.538$, $N = 72$, CI: −0.1640388 0.3114265).

Confirmation of Effects

We confirmed that the associations between brain network modularity at baseline and change in cognitive and scholastic performance remained significant in the physical activity group when controlling for age, sex, SES, IQ, pubertal timing, aerobic fitness, baseline performance, and in-scanner motion (mean of FD); Partial correlations between baseline modularity and change in performance for the children in the physical activity group: Executive Processes $r = 0.276$, $p = 0.023$; Cognitive Efficiency: $r = 0.401$, $p = 0.001$; Mathematics achievement: $r = 0.379$, $p = 0.001$.

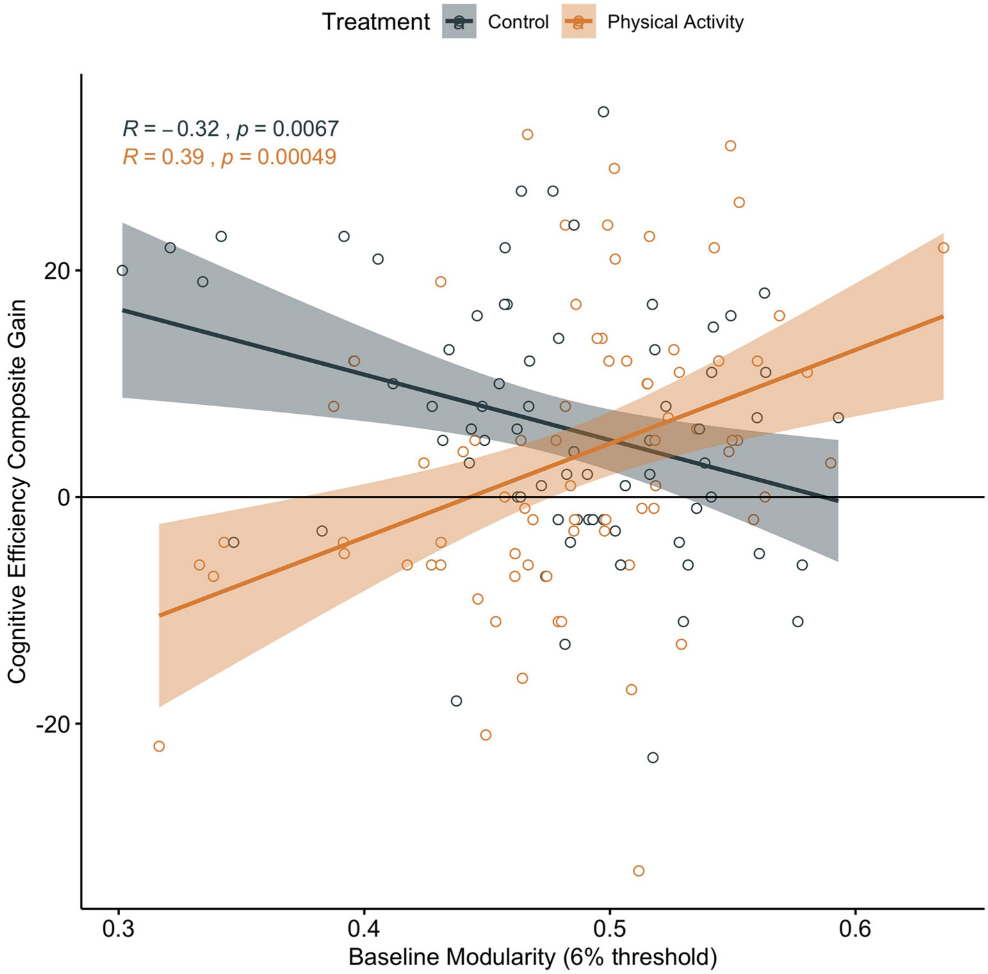

FIGURE 3 | Association between baseline brain network modularity and change in cognitive efficiency by group. Significant association in children involved in the physical activity intervention (uncorrected and corrected).

Bonferroni Correction

Note that when applying the Bonferroni correction for multiple comparisons (p = 0.05/6 tests; p = 0.0083), baseline modularity remained significantly associated with a change in Cognitive Efficiency and mathematics achievement in children involved in the physical activity intervention. Given the exploratory nature of our study which aimed to understand specific associations between brain network modularity and intervention-related changes in performance, we discussed all significant associations at both the Bonferroni-corrected and uncorrected levels.

DISCUSSION

Higher modularity of brain networks at baseline predicted greater improvements (changes) in cognitive performance (*via* cognitive performance clusters of executive function and cognitive efficiency) and scholastic performance (in particular, mathematics achievement) in children involved in an after-school physical activity intervention for 9 months. The relationships between baseline modularity and changes in performance were not present in a wait-list control group. The associations remained significant when accounting for age, sex, SES, IQ, pubertal timing, aerobic fitness, baseline performance, and in-scanner motion, which suggests that brain network modularity provides unique predictive information about intervention-related cognitive and academic progress during child development. Our results have important implications for biomarkers of cognitive plasticity in preadolescent children.

Our results generally support and extend previous research which demonstrates that brain network modularity at baseline predicts gains in cognitive performance in younger and older adults after cognitive and physical interventions (Arnemann et al., 2015; Gallen et al., 2016; Baniqued et al., 2018, 2019). Our extension of this research to children suggests that brain network modularity may predict cognitive changes

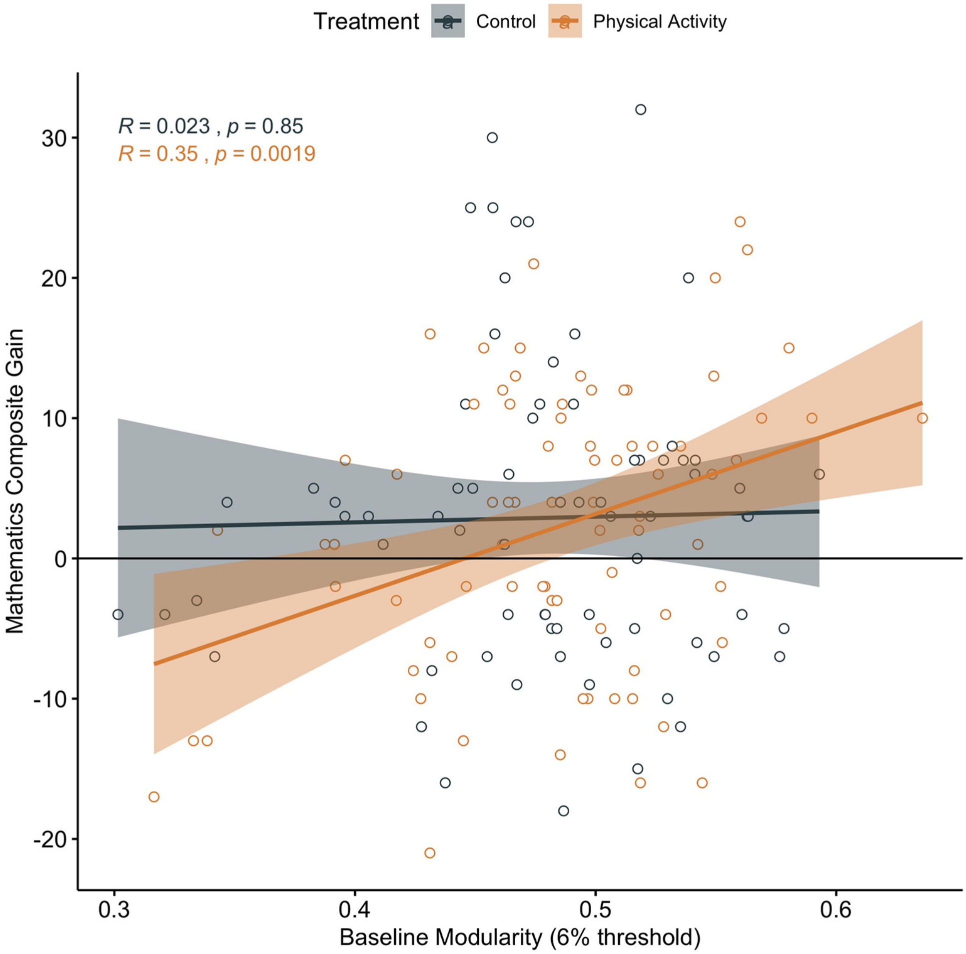

FIGURE 4 | Association between baseline brain network modularity and change in mathematics achievement by group. Significant associations in children involved in physical activity intervention (uncorrected and corrected).

via intervention in populations across the lifespan. We also extend the predictive power of brain modularity to other cognitive functions outside executive function, including the cognitive cluster of cognitive efficiency (which involves perceptual speed, short term memory, and the ability to store and recode information) as well as mathematics performance. Together, our data add to the framework of brain network modularity as a biomarker of plasticity and cognitive progress *via* interventions designed to improve cognitive and brain health (Gallen and D'Esposito, 2019). That is, global network properties and brain network architecture may capture individual differences in neuroplasticity that promote cognitive enhancement.

It is important to note that, unlike previous studies of modularity predicting intervention-related cognitive gains in young adults, older adults and TBI patients, relative to a control group (Arnemann et al., 2015; Gallen et al., 2016; Baniqued et al., 2018, 2019), physically active children in our study did not show significantly greater improvements in cognitive and scholastic performance compared to the wait-list control group, a group of typically developing children (age 7–9 years) across 9 months (i.e., lack of Group × Time interaction). That is, in our study, children in the physical activity intervention group and children in the wait-list control group showed statistically similar improvements in task performance across 9 months, perhaps due to practice effects and/or developmental effects that obscured potential benefits from the intervention. However, baseline modularity was only associated with changes in cognitive and academic performance in the physical activity group, not in the wait-list control group. As Gallen and D'Esposito (2019) suggest, modularity is a biomarker of intervention-related changes, so baseline modularity may have little predictive power for children not involved in a systematic multi-modal intervention. Indeed, the FITKids2 intervention was a multi-modal physical activity intervention, which included aerobically demanding activities as well as motor skills and health promotional activities. This intervention was different than the physical activity intervention in older adults, which involved walking around a track or dancing (Baniqued et al., 2018). Furthermore, the older adults in Baniqued et al. (2018) showed improvements in aerobic fitness levels with the physical activity intervention, unlike our study in which there were no significant effects of the physical activity intervention on aerobic fitness. As the physical activity dose provided in our intervention did not significantly modulate aerobic fitness levels, this may also help explain the lack of Group × Time interaction for all cognitive outcomes.

Computational models provide insight into the theoretical interpretations of the benefits of a modular network organization (Wig, 2017) as well as the association between modularity and neuroplasticity. For example, greater network modularity has been associated with better performance on memory tasks (Stevens et al., 2012; Chan et al., 2014), and brain modularity predicts rates of learning during working memory training (Iordan et al., 2018). Theoretically, individuals with a modular network organization may be able to apply small modifications and reconfigurations of specialized modules in response to new environments (e.g., interventions) to maximize performance (Kashtan and Alon, 2005). One research team compared functional connectivity during rest and during cognitive tasks to examine how changes in functional connectivity between rest and task contributed to cognitive performance (Schultz and Cole, 2016). Interestingly, instead of larger changes in functional connectivity reflecting optimization of networks during cognitive challenges, higher performers showed smaller changes in functional connectivity between rest and task, and network update efficiency correlated with intelligence (Schultz and Cole, 2016). These patterns suggest that small and efficient network updates may result in improved performance. As such, the results of the current study suggest that higher network modularity may represent an effective brain organization for predicting the progress of cognitive and academic performance with physical activity training during one school year.

More broadly, our results raise the possibility that brain network assessments in children may be used as biomarkers to guide the design and implementation of interventions to maximize effectiveness and improve outcomes. Metrics of modularity might be used to customize interventions, perhaps by personalizing intensity, frequency, and duration of physical activity for each child. For example, children with low baseline brain network modularity might require a longer or more vigorous physical activity intervention. Or, children with low baseline brain network modularity may not be at an optimal time point to benefit from an intervention. That is, it is possible that brain network modularity, to some degree, may signify a critical period of development when the developing brain is especially susceptible to intervention.

Future research is needed to determine how to maximize brain modularity at baseline to create optimal brain network properties to help individuals benefit from interventions. That is, what leads to increases in brain network modularity? It will also be important to understand the mechanisms by which brain modularity relates to changes in brain structure and function as well as neuronal health and vasculature with interventions. For example, in older adults, the upregulation of neurotrophic factors is associated with greater exercise-related changes in brain connectivity (Voss et al., 2013). Future studies might also include a longer resting-state scan–yet our scan (4 min, 6 s) was comparable to other brain modularity studies of varying resting-state scan length (4 min: Gallen et al., 2016; 5 min: Arnemann et al., 2015; 6 min: Baniqued et al., 2018, 2019). Furthermore, does brain network modularity predict changes in brain structure and brain function with interventions? Is the brain network modularity a biomarker for children with clinical disorders (e.g., Arnemann et al., 2015)? Do other network metrics such as global and local efficiency relate to changes in cognition? What subnetworks are contributing to the associations? For example, modularity in the association systems (e.g., default mode network, frontal-parietal network, dorsal attention network) has been shown to contribute to the association between modularity and intervention-related improvements in older adults (Gallen et al., 2016).

It will also be important to understand the specific cognitive processes predicted by modularity, as we do not report associations between baseline brain network modularity and changes in performance on tasks of thinking ability, verbal ability, or reading achievement. Indeed, our study was exploratory, as the first investigation to examine whether brain network modularity was a predictor of intervention-related changes in cognition and scholastic performance in children. As previous investigations have explored one cognitive outcome (executive function; Gallen et al., 2016; Baniqued et al., 2018, 2019) we aimed to understand whether modularity also predicted other cognitive abilities (e.g., cognitive efficiency, thinking ability), as well as school performance (e.g., mathematics, reading). Future studies should continue to dive into the specific associations between modularity and changes in intervention-related performance in populations across the lifespan as well as continue to consider multiple comparisons. Interestingly, the association between baseline modularity and change in executive function in children involved in the physical activity intervention was the one relationship that did not pass multiple comparison correction (unlike the significant associations between modularity and intervention-related changes in executive function in older adults; Gallen et al., 2016; Baniqued et al., 2018, 2019).

In conclusion, as trends indicate that children are becoming increasingly inactive and overweight, and physical activity opportunities are being reduced in schools, it is an important time to understand the associations among brain organization, cognitive and scholastic performance, and lifestyle factors such as physical activity. Interventions are designed for scientists and clinicians to better understand how to maximize neurodevelopmental processes important for cognitive performance and school achievement during childhood and across the lifespan. Given the time and cost to develop training interventions, it is important to develop biomarkers that predict how individuals respond to training as well as individual differences in cognitive and brain outcomes. It is of further importance to understand critical periods in the lifespan in which interventions may be especially effective. Here, we add to the evidence suggesting that brain network modularity, a measure of large-scale network organization, predicts change in cognitive function with an intervention, and we are the first to extend this framework to children.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board, University of Illinois at Urbana-Champaign. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

LC-H wrote the manuscript. LC-H, DC, CH, and AK conceived and designed the FITKids2 project and study. LC-H and TW analyzed the main outcomes of the present manuscript. LC-H, CK, ED, LR, S-CK, DW, and RW were involved in subject running and data organization of FITKids2 data. PB was included for experience with brain network modularity framework and feedback.

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Sustained Effects of Acute Resistance Exercise on Executive Function in Healthy Middle-Aged Adults

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The present study examined the sustained effects of acute resistance exercise on inhibitory function in healthy middle-aged adults. Seventy healthy middle-aged adults (mean age = 46.98 ± 5.70 years) were randomly assigned to exercise or control groups, and the Stroop test was administered before, immediately after, and 40 min after exercise. The resistance exercise protocol involved two sets of seven exercises performed for a maximum of 10 repetitions, with 60 s between sets and exercises. Acute resistance exercise resulted in higher Stroop test performance under the incongruent (inhibition) and interference conditions immediately post-exercise and 40 min post-exercise. Furthermore, the difference in scores after 40 min was significant. The findings indicate that a moderately intensive acute resistance exercise could facilitate Stroop performance and has a more beneficial effect on sustaining of cognition that involves executive control at least 40 min.

Keywords: inhibitory control, executive function, resistance exercise, sustained effects, middle-aged adult

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INTRODUCTION

Cognitive ability is important for daily life as a main component of the health-related quality of life. However, the most impactful change in cognition with increasing age is declining executive function (EF), with cognitive impairments severe enough to impair their everyday functional abilities (Barnes, 2015; Murman, 2015). Encompassing a set of higher-order cognitive processes, EF enables individuals to plan, organize, and complete tasks when engaging in goal-directed actions and adaptive responses to novel or complex situations (Hillman et al., 2012). Age-related decline of EF is the focus of numerous studies on cognitive aging (Salthouse, 2010; Chang et al., 2012b; Lustig and Jantz, 2015; Fjell et al., 2017; Rey-Mermet and Gade, 2018), particularly in inhibitory control among middle-aged adults (Chang and Etnier, 2009b; Chang et al., 2014, 2019), which could be improved via physical activity, such as acute aerobic or resistance exercises (Byun et al., 2014; Chang Y. K. et al., 2017).

According to meta-analyses of exercise and inhibitory control, acute aerobic or resistance exercises have small to moderate effects on inhibitory control in middle-aged populations (Yanagisawa et al., 2010; Chang et al., 2012b; Basso and Suzuki, 2017). Notably, in contrast to aerobic exercise, concentration levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) are strongly associated with the degree of resistance exercise intensity (Gregory et al., 2013), and increases in these concentrations are correlated with inhibitory control improvements (Tsai et al., 2014). Furthermore, a systematic review provides compelling evidence for the occurrence of acute resistance exercise-induced increases in inhibitory control performance (Wilke et al., 2019). Inhibitory control refers to the ability to control one's attention, behavior, thoughts, or emotions to override a strong internal predisposition or external lure while irrelevant information in the interference control and inhibit a prepotent response to allow selection of the appropriate responses (Diamond, 2013). Several studies have observed improvements on inhibitory control after an acute bout of resistance exercise (Chang and Etnier, 2009a; Chang et al., 2014; Johnson et al., 2016; Naderi et al., 2019; Wilke et al., 2019). Although the findings generally support a beneficial immediately effect of acute resistance exercise on cognitive performance (Chang and Etnier, 2009b; Forte et al., 2013; Chang et al., 2014, 2019; Naderi et al., 2019). The few studies that have examined the delayed effects (post-training) on cognitive performance have concluded that the benefits are not maintained (Pontifex et al., 2009; Barella et al., 2010; Chang et al., 2019; Naderi et al., 2019). Thus, whether an acute bout of resistance exercise exerts a sustained effect on inhibition in middle-aged individuals remains to be clarified.

In reviewing the literature on sustained effects of resistance exercise on inhibitory control, Chang and Etnier (2009a) and Chang et al. (2014) both observed facilitation of performance immediately after exercise relative to a control condition on a Stroop task. Furthermore, Naderi et al. (2019) observed that the exercise-induced gains on inhibitory control were larger at 15 min than 180 min after an acute resistance exercise. No such effect was observed for a low-intensity resistance exercise bout, indicating that a moderate-intensity resistance exercise bout was beneficial to inhibitory control. Tsukamoto et al. (2017) observed similar facilitative yet immediate effects of resistance exercise on inhibition relative to a pre-exercise condition. Further support for the beneficial effects of acute exercise on inhibitory control has been garnered from Johnson et al. (2016) who observed facilitation in performance on a Stroop Test after a 30-min recovery period after exercise, but not following a delay of 30 or 60 min. Taken together, these results suggest that changes in inhibitory control could be similar facilitative benefits after 30 min of resistance exercise relative to a pre-exercise condition. These inconsistencies regarding sustained effects expose a lack of clarity regarding the influence of resistance exercise on inhibitory control (Barella et al., 2010; Naderi et al., 2019). Despite these initial inquiries into the immediate benefits of acute resistance exercise for inhibitory aspects of executive control, little research has investigated its sustained effects over time (Barella et al., 2010; Naderi et al., 2019).

Despite these initial inquiries into the effect of acute exercise on inhibitory aspects of executive control, little research has examined this relationship of the time course to the cognitive benefits. Therefore, a rationale is raised for our current theoretical understanding for the acute exercise intensity-cognition interaction based on the arousal-performance interaction theory. A prominent theoretical framework proposed by Davey (1973) revealed that exercise intensity, and its effect on arousal, influences cognitive performance in an inverted-U manner. Specifically, inhibitory control was benefited by moderate-intensity exercise compared to low-intensity exercise (Tsukamoto et al., 2017; Naderi et al., 2019). In addition, the critical indicators of psychophysiology such as insulin-like growth factor, brain-derived neurotrophic factor, fibroblast growth factor 2, and vascular endothelial growth factor (Chang et al., 2012b; Tsai et al., 2014) suggested that moderate-intensity resistance exercise influences cognition performance by optimally elevating arousal.

The purposes of this study was to examine the immediate and sustained effects of acute resistance exercise on inhibition at 5 and 40 min post-exercise after an acute resistance exercise. A previous meta-analysis reported that the largest effects of exercise on cognitive performance could generally be observed during a period of 11–20 min after exercise (Chang et al., 2012a). However, the latter time point was selected based on two lines of evidence. The time point of 5 min immediately post-exercise was selected based on a physiological stimulus for acute increases in GH and IGF-1 levels (Gregory et al., 2013). On other hand, the time point of the 40 min post-exercise was selected due to reductions in state anxiety during processes that influenced cognition. Previous studies have most commonly examined cognition during the initial 17 to 60 min post-exercises to determine acute exercise effects on cognition (Johnson et al., 2016; Tsukamoto et al., 2017). We, therefore, chose 5 min immediate post-exercise as the time point to reflect the more effects of acute exercise on inhibitory control performance. The purpose of this study was to extend the literatures by including immediately post-exercise and 40-min post-exercise that are theoretically and biologically justifiable, and also focusing on changes in inhibitory control performance after an acute resistance exercise. Therefore, we hypothesized that healthy middle-aged adults participating in acute resistance exercise would exhibit immediate improvement in inhibitory control compared with those not participating in the exercise treatment and that effects would be sustained at least 40 min.

MATERIALS AND METHODS

Participants

A total of 70 community-dwelling healthy adults, aged 40–60 years, were initially recruited in Taipei, Taiwan. The potential participants were included if they met the following criteria: (1) they met the requirements of the physical activity readiness questionnaire (PAR-Q), to ensure their safety when performing a single bout of exercise and (2) they achieved a score of more than 26 on the Chinese version of the mini-mental state examination (MMSE), verifying that they may be considered cognitively normal (Guo et al., 1988). The exclusion criteria were as follows: (1) the presence of comorbid conditions, such as autism spectrum disorder, attention deficit hyperactivity disorder, intellectual disability, and serious affective disorder; (2) history of brain injury or neurological disorder; and (3) medical conditions involving the presence of any neurological, psychiatric, musculoskeletal, or cardiovascular problems that would affect exercise ability. After assessment, the participants were randomly assigned to an exercise group (n = 35) or a control group (n = 35) by drawing lots. Detailed characteristics of the participants are presented in **Table 1**. The study protocol, informed consent, and all materials were reviewed and approved by a university's Institutional Review Board in Taipei prior to the experiment.

TABLE 1 | Summary of the demographic characteristics of the participants.

Variables/Sex/Groups		EG (*n* = 35)	CG (*n* = 35)	Total
Sex (M: F)		15:20	16:19	31:39
Age (years; *M* [SD])	Male	45.97 [5.57]	45.59 [4.24]	
	Female	46.72 [5.51]	49.22 [6.75]	46.98 [5.70]
	Total	46.39 [5.47]	47.56 [5.95]	
Height (cm; *M* [SD])	Male	172.53 [4.61]	172.50 [3.90]	
	Female	160.15 [5.29]	158.32 [3.86]	165.12 [7.98]
	Total	165.46 [7.94]	164.80 [8.12]	
Weight (kg; *M* [SD])	Male	73.95 [5.81]	77.43 [13.79]	
	Female	57.05 [5.88]	53.28 [4.76]	64.30 [13.14]
	Total	64.29 [10.25]	64.32 [15.65]	
Body mass index (kg/m^2; *M* [SD])	Male	24.85 [1.85]	25.84 [4.12]	
	Female	22.22 [1.70]	21.28 [2.00]	23.36 [3.12]
	Total	23.35 [2.19]	23.37 [3.86]	
Education (years; *M* [SD])	Male	17.20 [2.08]	17.06 [2.62]	
	Female	15.80 [1.82]	15.05 [3.32]	16.19 [2.64]
	Total	16.56 [2.53]	17.06 [2.62]	
Resting HR (bpm)	Male	73.60 [6.49]	72.63 [2.58]	
	Female	71.50 [5.47]	70.37 [4.23]	71.90 [4.94]
	Total	72.40 [5.93]	71.40 [3.70]	
Mini-mental state examination	Male	28.66 [0.82]	28.56 [0.89]	
	Female	28.45 [0.99]	28.47 [0.90]	28.53 [0.90]
	Total	28.54 [0.92]	28.51 [0.87]	
Resistance exercise				
Biceps curl-right (lb)	Male	39.07 [6.39]	∼	34.63 [6.16]
	Female	3130 [3.24]	∼	
Biceps curl-left (lb)	Male	35.73 [5.12]	∼	32.77 [5.50]
	Female	30.55 [4.76]	∼	
Back lat pull down (lb)	Male	88.93 [4.38]	∼	79.46 [9.34]
	Female	72.35 [4.22]	∼	
Chest fly (lb)	Male	53.87 [5.42]	∼	40.17 [13.36]
	Female	29.90 [6.23]	∼	
Chest press (lb)	Male	84.67 [9.33]	∼	61.69 [21.84]
	Female	44.45 [7.74]	∼	
Leg curl (lb)	Male	79.47 [10.22]	∼	66.09 [14.02]
	Female	56.05 [5.22]	∼	
Leg press (lb)	Male	175.20 [9.34]	∼	163.26 [13.41]
	Female	154.30 [7.78]	∼	

Measures

Stroop Test

The Stroop test was developed by the Vienna Test System. The Vienna test system is a test system for computerized executive function assessments. With it, digital tests of executive function can be administered and it provides automatic and comprehensive scoring. It includes a series of computerized tasks. Perceptual motor speed is measured when reading color words (e.g., "red," "yellow," "blue," or "green") and naming the color that the word is (or is not) written in. The test uses correct responses on time as reaction time. The test has 128 trials, with 5 trials for practice. Trials present the four types of Stroop task, namely, the baseline of reading words and naming colors as the congruent condition, and reading and naming words under the incongruent condition; the difference in reaction time between the conditions is the interference tendency and is referred to as the Stroop effect. A positive value indicates an increased interference tendency, whereas a negative value is characteristic of a reduced interference tendency. In the congruent condition, the reading word and naming color stimulus is displayed in the color matching the meaning of the word (e.g., the word "red" is presented in red color). In the incongruent condition, the reading word stimulus is displayed in a color matching the meaning of a different stimulus (e.g., the word "yellow" is displayed in blue color). The participants must read the word (i.e., "yellow") aloud and disregard the color of the word is written in (i.e., blue). Alternatively, with the naming color stimulus, the participant must state the color of the word (e.g., "red") and disregard the word's meaning (e.g., the color green). The stimuli for each condition were displayed on a 15-inch laptop screen, and the test length was approximately 8 to 10 min. The validity and reliability of the Stroop test has been extensively reported (Scarpina and Tagini, 2017; Erdodi et al., 2018). The Stroop test was chosen for the present study based on past evidence that it is both sensitive to the effects of exercise and provides a reliable measure of EF for healthy middle-aged adults (Chang and Etnier, 2009a).

Exercise Manipulation Check

Heart Rate

A Polar watch (Cybex 770T's CardioTouch, United States) was worn by each participant to measure the participant's heart rate (HR) during the resistance exercise stage, with the HR data from the HR monitor being recorded at 1-min intervals. HR data were assessed as an indicator of the physiological arousal induced by the resistance exercise. Four HR variables were identified: pre-exercise HR, treatment HR, immediately post-exercise HR, and 40-min post-exercise HR. Pre-exercise HR was determined 60 s before the performance of the first Stroop test (pre-exercise); the treatment HR was the average HR during the moderate intensity or control treatment; and the immediately post-exercise HR and 40-min post-exercise HR were assessed 60 s before the participant performed the Stroop tests for immediately post-exercise and 40 min post-exercise, respectively.

Rating of Perceived Exertion

Each participant completed the rating of perceived exertion (RPE), which was defined as their perception of their own level of effort during the exercise. According to the original scale by Borg (1998), the RPE rates a participant's perceived exertion on a scale of 6 ("very, very light to fairly light exertion") to 20 ("maximal exertion"). The RPE was recorded at 2-min intervals during the exercise.

Resistance Exercise Design

The participants were instructed to avoid engaging in any other resistance exercise training or any other physical activities such as jogging, running, yoga, dance, tennis, or table tennis for a week before the experimental session. The 10-repetition maximum (RM) represents the maximum weight an individual can successfully lift in 10 repetitions and approximates 70% of the 1-RM. After stretching, the participants were asked to warm up with light resistance exercise for 10 min, and were then instructed to change the load and to continue the testing process until they reached a load level that they would be able to lift for a maximum of 10 repetitions. Generally, the instructor was able to adjust the loads such that the 10-RM could be measured within four testing sets. The following seven muscle exercises were selected: the bench press, shoulder press, dumbbell rows, alternating bicep curls, triceps pushdowns, leg extensions, and leg curls (American College of Sports Medicine (ACSM), 2013). The load for each of the exercises was determined using the same protocol. The resistance exercise consisted of two sets of 10-RM tests for the seven resistance exercises with 60 s of rest between sets and exercises. The protocol was selected based on previous studies (Chang et al., 2014; Tsai et al., 2014) that have indicated that cognitive performance could be affected positively by using this protocol. HR and RPE, two commonly used indicators for exercise intensity in EF studies, were used to confirm that the participants achieved moderate exercise intensity (Chang et al., 2019).

Procedures

The participants were requested to visit the Sport Pedagogy Laboratory on two separate testing days at least 48 h apart. Trained laboratory researchers administered questionnaires regarding the inclusion criteria, the 10-RM tests for each of the seven muscle groups, and the Stroop tests. On Day 1, each participant was invited to visit the laboratory at the confirmation stage and was presented with a brief introduction to the experiment. The informed consent form, MMSE, PAR-Q, and medical health history questionnaire were given to them to read and complete. After completing the questionnaires on Day 1, each participant was asked to sit quietly, individually, on a comfortable sofa in a dimly lit room for 15 min and instructed to attach the HR monitor. After the 15-min period, the HR baseline was recorded, and the participant's 10-RM for each of the muscle groups was determined. The participants were told to avoid the use of stimulants such as caffeine the day before and the day of the tests.

On Day 2, each participant was again asked to sit quietly, individually, on a comfortable sofa in a dimly lit room for 15 min. Then, pretest scores for the Stroop test were collected, and the participant was asked to press the correct color button on the keyboard for each stimulus in each condition. In the exercise groups, the participants then warmed up for 10 min and conducted the resistance exercises for 25–30 min. At the start of each session, the participants were fitted with a Polar Cybex 770T's CardioTouch HR monitor to assess their physiological arousal and the effects of the selected intensities on cardiovascular responses. Subjective RPE was collected after each set of exercises using a category-interval rating scale ranging from 6 (no exertion at all) to 20 (maximal exertion). In the control group, the participants were instructed to sit quietly in a well-lit room and read exercise-related magazines for 30 min.

Immediately post-exercise (3 to 5 min after the end of the session), we asked each participant to complete the Stroop test again using the same directions and under the same conditions as the pre-exercise test. Afterward, the participant rested for 30 min and then completed all four conditions of the Stroop test again (40-min post-exercise stage). Each of the participants was given US$20 as compensation for participating in the study and was debriefed by a member of the research team.

RESULTS

Demographic Analyses

To ensure homogeneity of potential confounders between the control and exercise groups, an analysis of independent samples was applied using a t-test or a χ^2 test to compare demographic data and pre-exercise variables with continuous and discrete scales, respectively, between the groups. The analyses indicated no significant differences between the groups for age ($t = -0.85$, $p = 0.39$), height ($t = 0.34$, $p = 0.73$), weight ($t = -0.01$, $p = 0.99$), BMI ($t = -0.23$, $p = 0.99$), years of education ($t = 0.67$, $p = 0.50$), resting HR ($t = 0.85$, $p = 0.40$), or MMSE score ($t = 0.13$, $p = 0.90$). Furthermore, no differences were observed for sex ratio ($\chi^2 < 0.91$, $p = 0.33$). Descriptive data are summarized in **Table 1**.

Exercise Manipulation Check

One-way repeated ANOVA was used to analyze HR in the exercise group, and the results revealed a significant time effect ($F_{(3,32)} = 1027.75$, $p < 0.0001$, partial $\eta^2 = 0.99$), indicating that the treatment HR was significantly higher than the immediately post-exercise HR and the follow-up HR, which was also significantly higher than the pre-exercise HR. The average RPE value during the resistance exercise was 15.25 ± 1.46. Descriptive data for the exercise manipulation check are summarized in **Table 2**.

Effects of Resistance Exercises on Stroop Performance

In the congruent condition of reading words and naming colors, the 2×3 mixed ANOVA revealed a significant Time effect ($F_{(2,67)} = 16.14$ and 13.13, $p < 0.0001$, partial $\eta^2 = 0.33$ and 0.28) and significant interactions of Group with Time ($F_{(2,67)} = 5.06$ and 4.66, $p < 0.01$, partial $\eta^2 = 0.13$ and 0.12). However, no

TABLE 2 | Descriptive data for the exercise manipulation check.

Variables	EG (M [SD])	CG (M [SD])
Pre-exercise HR (bpm)	73.66 [2.91]	72.86 [1.77]
Treatment HR (bpm)	122.74 [4.15]	73.86 [2.37]
Immediately post-exercise HR (bpm)	97.69 [2.76]	74.17 [2.04]
40-min post-exercise HR (bpm)	89.71 [4.06]	73.83 [3.15]
RPE	15.26 [1.46]	~

bpm, beats per minute; HR, heart rate; RPE, rating of perceived exertion.

significant Group effect was observed ($F_{(1,68)}$ = 0.41 and 0.01, $p > 0.05$). Follow-up decompositions indicated significant Time effects for the congruent condition of reading words and naming colors in the exercise group ($F_{(2,33)}$ = 13.21 and 11.44, $p < 0.001$, partial η^2 = 0.45 and 0.41), wherein pairwise comparisons revealed that the participants exhibited faster reaction times (RTs) in the immediately and 40-min post-exercise tests than in the pre-exercise test. No RT difference was observed between the two post-exercise tests. As expected, no significant Time effects were observed for the congruent condition of reading words and naming colors in the control group ($F_{(2,33)}$ = 2.96 and 1.92, $p > 0.05$). The results under the congruent condition are presented in **Figures 1A,B**.

To test the hypothesis regarding the effects of acute resistance exercise on the incongruent condition of reading words and naming colors, we conducted 2 × 3 mixed ANOVA. The results revealed significant Time effects ($F_{(2,67)}$ = 17.06 and 13.80, $p < 0.0001$, partial η^2 = 0.34 and 0.29) and significant interactions of Group with Time ($F_{(2,67)}$ = 9.67 and 10.88, $p < 0.0001$, partial η^2 = 0.22 and 0.25). The results also indicated a significant Group effect ($F_{(1,68)}$ = 4.22 and 4.22, $p < 0.05$, partial η^2 = 0.06 and 0.06). The exercise group exhibited faster RTs than the control group did in the incongruent condition of reading words and naming colors immediately post-exercise and 40-min post-exercise ($t_{(68)}$ = −3.04, −3.96, −3.02, and −3.07, $p < 0.01$). Follow-up decompositions indicated significant Time effects for the exercise group under the incongruent condition of reading words and naming colors ($F_{(2,33)}$ = 20.72 and 20.64, $p < 0.001$, partial η^2 = 0.56 and 0.56), wherein pairwise comparisons revealed that the participants again exhibited faster RTs immediately and 40-min post-exercise than at pre-exercise, and no significant difference was noted between the post-exercise scores. As expected, no significant Time effects were observed for the incongruent condition of reading words and naming colors in the control group ($F_{(2,33)}$ = 1.33 and 0.24, $p > 0.05$). The RTs under the incongruent condition are presented in **Figures 1C,D**.

To test the hypothesis regarding the effects of acute resistance exercise on the interference tendency of reading words and naming colors as indicators of inhibitory control, we conducted 2 × 3 mixed ANOVA. The results revealed significant Time effects ($F_{(2,67)}$ = 5.04 and 3.49, $p < 0.01$, partial η^2 = 0.13 and 0.10) and significant interactions of Group with Time under the interference conditions ($F_{(2,67)}$ = 6.36 and 4.01, $p < 0.05$, partial η^2 = 0.11 and 0.11). A significant Group effect was also observed ($F_{(1,68)}$ = 26.07 and 47.19, $p < 0.001$, partial η^2 = 0.27 and 0.41). Notably, the exercise group had shorter RTs than the control group immediately and 40-min post-exercise ($t_{(73)}$ = −5.17, −5.29, −5.04, and −6.07, $p < 0.001$). Follow-up decompositions indicated significant Time effects for the exercise group ($F_{(2,33)}$ = 13.52 and 6.38, $p < 0.01$, partial η^2 = 0.45 and 0.28), wherein pairwise comparisons revealed that the participants exhibited faster RTs in the post-exercise tests than in the pre-exercise test; no significant RT difference was observed between the two post-exercise tests. As expected, no significant Time effects were observed for the control group ($F_{(2,33)}$ = 1.17 and 0.08, $p > 0.05$). The results suggested that the responses of the exercise group were quicker both immediately post-exercise and 40-min post-exercise compared with those pre-exercise. They were also significantly quicker than those of the control group. The RTs for the interference tendency are presented in **Figures 1E,F**.

DISCUSSION

This study examined the effects of a bout of acute resistance exercise on inhibition performance in healthy middle-aged adults – specifically, the sustained effects of resistance exercise on the results of the Stroop test, which measures EF inhibition and attention. Exercise intensity was assessed using HR and RPE; HR was increased during the exercise session, immediately post-exercise, and 40 min post-exercise, reflecting physiological arousal. The participants in the exercise group had superior performance in RT under the interference condition and interference tendency immediately and 40 min post-exercise relative to the control group. These findings suggest that moderate-intensity resistance exercise has a beneficial effect on inhibition immediately post-exercise and 40 min post-exercise.

The findings are consistent with those of previous studies indicating that acute moderate-intensity resistance exercise has advantageous effects on the results of the congruent and incongruent conditions (Chang and Etnier, 2009a,b; Tsai et al., 2014; Chang et al., 2019; Naderi et al., 2019). Given that neuroimaging techniques have indicated that the prefrontal cortex supports regulative control processes and is likely the neural substrate for the improved Stroop performance elicited by moderate resistance exercise (Chang Y. K. et al., 2017). One possible interpretation for the positive effects of acute resistance exercise on inhibitory control is that they might be related to the plasma levels of neurochemicals such as brain-derived neurotrophic factor and catecholamine (Ramel et al., 2004; French et al., 2007; McMorris et al., 2008). Findings regarding resistance exercise in middle-aged individuals suggest that such exercise could stimulate increases in HR and changes in catecholamine levels and that such changes might explain the general facilitation of performance under all Stroop test conditions associated with resistance exercise (French et al., 2007; Chang and Etnier, 2009a,b). At the same time, resistance exercise may result in increased HR and may stimulate the secretion of catecholamine, with elevated levels of catecholamine being sustained 40 min after acute resistance exercise, which might, in turn, provide optimal force and energy supplementation.

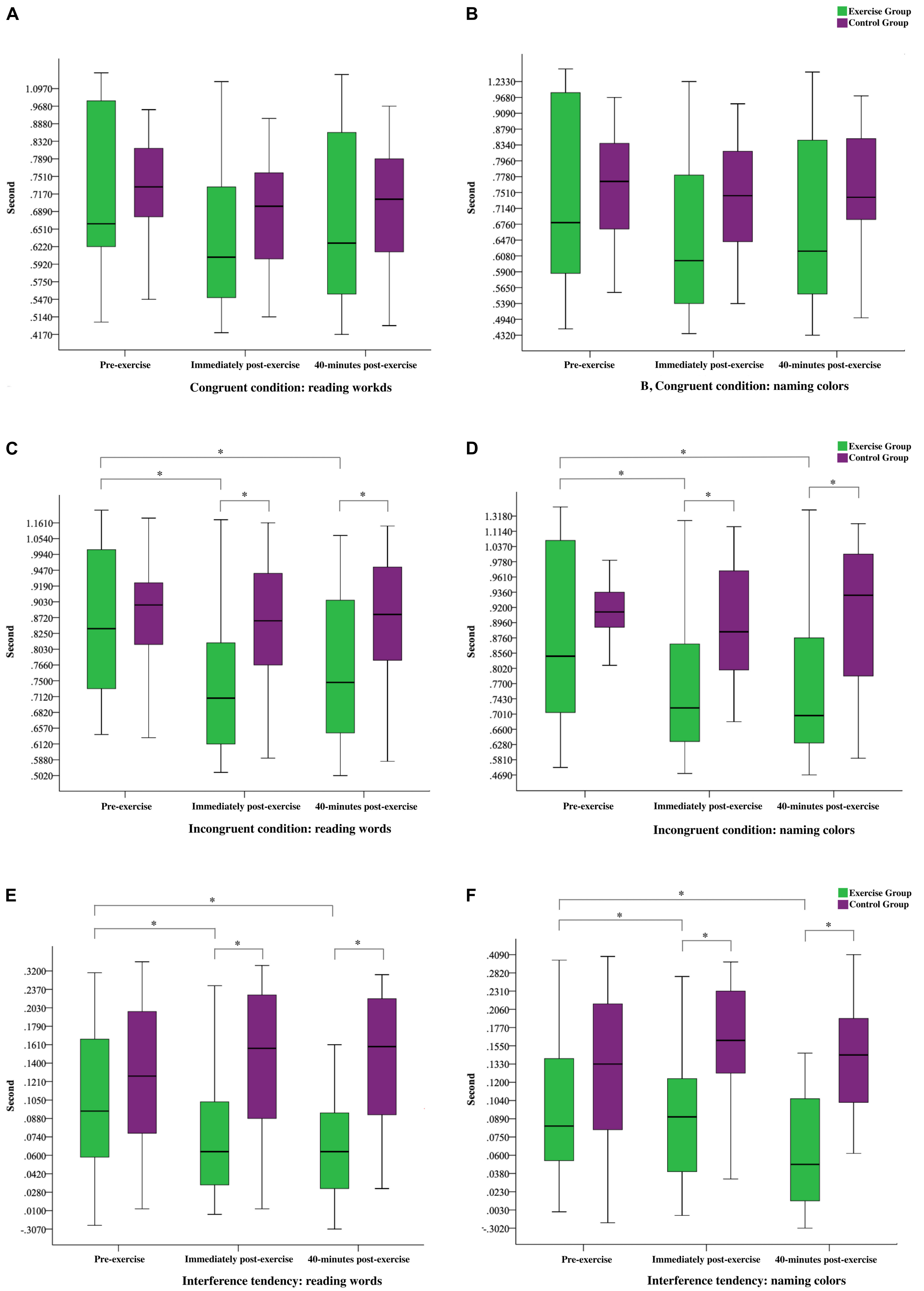

FIGURE 1 | Stroop test performance on the pre-exercise, immediately post-exercise, and 40-min post-exercise; green indicates exercise group and purple indicates control group * indicates a significant difference (p < 0.05) between the exercise and control groups or between pre-exercise, immediately post-exercise, and 40-min post-exercise.

However, the present hypothesis concerned whether the effect on inhibitory control would be sustained 40 min after the termination of acute resistance exercise. We observed an effect immediately after exercise, and the performance of the exercise group across a variety of the Stroop tasks supported the hypothesis of a sustained effect, because the beneficial effect in the exercise group compared with the control group was sustained for at least 40 min. The exercise group had high HR levels 40 min after the termination of exercise compared with the control group, although the arousal levels were much lower than those during and immediately after the exercise, suggesting that the mechanisms that mediate the immediate and sustained effects after the termination of exercise might explain the sustained effect. This finding could be explained by the cognitive-energetic model that the optimal arousal levels drive cognitive performance (Sanders, 1983). In our study, the intervention of acute resistance exercise induced an increase in HRs that may be related to the exercise-induced increase in arousal and lead to improved reaction time in inhibitory control. Furthermore, the inhibitory control performance was assessed immediately post-exercise while the heart rate was closed to moderate arousal level. Although, the exercise-induced arousal level would decrease with time, the effects were still sustained at 40-min post-exercise. Therefore, our study results supported and agreed with the cognitive-energetic model that resistance exercise has an immediate benefit on inhibition and the benefit can be sustained 40 min after the termination of acute exercise.

After the cessation of resistance exercise, the participants had higher levels of arousal immediately and 40 min post-exercise compared to the control group, while these arousal levels were significantly lower than those during exercise and immediately after the cessation of resistance exercise. Indeed, moderate exercise intensity may induce an optimal state of physiological arousal (e.g., heart rate) that is associated with facilitated inhibitory control performance (Kashihara et al., 2009). Although, the mechanisms could mediate the effects of resistance exercise immediately after the termination of resistance exercise. Nevertheless, previous studies by Chang Y. K. et al. (2017), Drollette et al. (2014), and Hillman et al. (2009) provided potential explanations for this discrepancy by using neuroelectric approaches. They have used event-related potentials (ERPs) to observe that cognition after acute exercise–induced arousal returned to within 10% of pre-exercise levels to avoid any general arousal effects on ERP measures stemming from exercise participation. Acute exercise elicited brain activation by increasing P3 amplitudes, shortening P3 latencies, or decreasing N450 latency during the performance of an executive control task. Their results suggested that attentional resource allocation and information processing efficiency during cognitive performance were promoted by acute exercise, moderate-intensity exercise may result in an optimal amount of resources. We designed the current study because examination of Stroop performance and exercise-induced arousal immediately post-exercise and 40 min post-exercise is necessary, and is to certain the relationship of the time course and resistance exercise to the benefit of inhibitory control. Protocols examining different time points provide information regarding the immediate effects of exercise on inhibitory control and indicate how long the effects continue; moreover, they reveal the role of arousal in the relationship between acute exercise and inhibitory control in middle age. Therefore, an active lifestyle has a protective effect on healthy brain function in older adults (Rolland et al., 2010). Acute resistance exercise is a potential preventive strategy that might benefit brain function by delaying the onset of cognitive decline and slowing brain disease progression; however, well-designed randomized controlled trials are required. Finally, with population aging, declines in EF performance among middle-aged healthy adults, associated with appropriate capacity for daily living skills, are of concern. Our findings support the benefits of resistance training for inhibitory control. Ascertaining appropriate prescriptions of moderate-intensity resistance exercise for maximizing these effects is desirable.

Limitations and Future Research

This study had limitations that warrant caution with respect to the interpretation of its results and future research. Nonetheless, based on the findings of the present study, further research efforts in this field are suggested. First, the outcome of the study may have been affected by the small size and diversity of the sample; however, given the significance and size of the effects, we believe that a larger sample size would not have significantly altered the outcome. Second, an additional limitation of these data is the inability to gain a mechanistic understanding of the effects of acute resistance exercise on inhibitory control. That is, despite the interesting and positive sustained impacts about RT observed herein, little is known regarding which accuracy of interference condition and interference tendency on Stroop Test was influenced by an acute resistance exercise bout. Third, future studies should be designed to further our understanding of the measurement of intra-subject variation (i.e., standard deviation and coefficient of variation) for RTs. Meanwhile, the recording of ERPs could be used to explore stimulus and response conflicts within the processes underlying standard deviation and coefficient of variation for RTs. Whether standard deviation and coefficient of variation for RTs are related to localized brain regions is unknown, and neuroimaging could provide clarification. Because the intra-subject variation in RTs is a measure of a subject's consistency in responding to the conditions of congruent and incongruent stimuli, often quantified as the standard deviation and coefficient of variation of intra-subject variation across a task period; higher intra-subject variation, reflect in larger standard deviations, is associated with greater variability, or inconsistency, of responses. Finally, resistance exercise training and arousal-induced alterations in lateral prefrontal cortex neural activity (Yanagisawa et al., 2010), biochemical release (Hillman et al., 2009; Chang et al., 2014), and cerebral blood flow (Chang H. et al., 2017) have been posited. Future investigations regarding the relationships between resistance exercise, cognitive performance, and biophysiological mechanisms in middle-aged adults are necessary.

CONCLUSION

Our findings suggest that moderate-intensity resistance exercise promotes EF in healthy middle-aged adults. In summary, this study has extended the literature by providing evidence that acute resistance exercise has positive, sustained impacts on multiple cognitive functions, as assessed by the Stroop test, in healthy middle-aged adults. Furthermore, the results suggest that moderate-intensity resistance exercises have positive impacts and sustained effects on particular types of EF in middle-aged adults, with those impacts being larger under task conditions that place greater demands on inhibitory control cognition.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Taipei's Institutional Review Board (IRB-2020-011). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

C-CC and C-JH contributed to conception and design of the study and wrote sections of the manuscript. M-CH and Y-HC organized the database. W-YW and M-YH performed the statistical analysis. C-CC, M-CH, Y-HC, W-YW, MY-H, and C-JH wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Frequent, Short Physical Activity Breaks Reduce Prefrontal Cortex Activation but Preserve Working Memory in Middle-Aged Adults: ABBaH Study

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Prolonged sitting is increasingly common and may possibly be unfavorable for cognitive function and mood. In this randomized crossover study, the effects of frequent, short physical activity breaks during prolonged sitting on cognitive task-related activation of the prefrontal cortex were investigated. The effects on working memory, psychological factors, and blood glucose were also examined, and whether arterial stiffness moderated prefrontal cortex activation. Thirteen subjects (mean age 50.5 years; eight men) underwent three 3-h sitting conditions, interrupted every 30-min by a different 3-min break on separate, randomized-ordered days: seated social interactions (SOCIAL), walking (WALK), or simple resistance activities (SRA). Arterial stiffness was assessed at baseline. Before and after each 3-h condition, psychological factors (stress, mood, sleepiness, and alertness) were assessed through questionnaires and functional near-infrared spectroscopy (fNIRS) was used to measure changes in prefrontal oxygenated hemoglobin (Oxy-Hb), indicative of cortical activation, while performing working memory tasks [1- (baseline), 2-, and 3-back]. Blood glucose levels were continuously measured throughout the conditions. Results revealed no significant changes in Oxy-Hb during the 2-back compared with the 1-back test in any condition, and no time-by-condition interactions. During the 3-back test, there was a significant decrease in Oxy-Hb compared with the 1-back after the WALK condition in the right prefrontal cortex, but there were no time-by-condition interactions, although 3-back reaction time improved only in the WALK condition. Mood and alertness improved after the WALK condition, which was significantly different from the SOCIAL condition. Arterial stiffness moderated the effects, such that changes in Oxy-Hb were significantly different between WALK and

SOCIAL conditions only among those with low arterial stiffness. Blood glucose during the interventions did not differ between conditions. Thus, breaking up prolonged sitting with frequent, short physical activity breaks may reduce right prefrontal cortex activation, with improvements in some aspects of working memory, mood, and alertness.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier NCT04137211.

Keywords: cerebral blood flow, cognition, functional near-infrared spectroscopy, exercise, sedentary

INTRODUCTION

Sedentary behavior (defined as an energy expenditure of <1.5 METs while lying, sitting, or reclining, while awake (Tremblay et al., 2017)) can be detrimental for cognitive performance (Falck et al., 2017), whereas acute physical activity breaks may elicit positive effects (Carter et al., 2018). One of the main underlying mechanisms driving the acute physical activity-induced improvements on cognitive performance is assumed to be changes in cerebral blood flow driven by neural activation (Pontifex et al., 2019; Chandrasekaran et al., 2021). Previous research findings have demonstrated that a single bout of physical activity (about 10–20 min) can increase such task-related cerebral blood flow, with coinciding improvements in prefrontal cortex-dependent cognitive tasks (Herold et al., 2018). However, decreases in task-related cerebral blood flow after an exercise bout with concomitant enhancement in cognitive performance has also been observed (Murata et al., 2015; Moriarty et al., 2019). Thus, more studies are needed to understand the effects of acute physical activity on neural task-related changes in cerebral blood flow as a measure of cortical activation.

Moreover, the effects of a single bout of 10–20 min exercise of moderate-to-vigorous intensity on cognitive and psychological well-being are unlikely to compensate for a whole day of sitting. Frequent (every 20–30 min), short (approximately 1–3 min) physical activity breaks throughout the workday may be a more feasible strategy to offset the negative effects of prolonged sitting on cognitive performance and cerebral blood flow. Indeed, these types of breaks have been shown to be beneficial for central and peripheral vascular function (Loh et al., 2020), which are also compromised by prolonged sitting, but their effects on cortical activation remain unknown. Resistance exercise breaks may also improve vascular function (Dempsey et al., 2016a,b), which in turn may help in the maintenance of cerebral blood flow and cognitive function by means of reducing glycemic excursions throughout the day (Wheeler et al., 2017). Indeed positive effects have also been seen on executive function from acute resistance exercise (Tsukamoto et al., 2016; Pontifex et al., 2019). Thus, exercise breaks of different intensities may not only benefit vascular function, but also has the potential to improve cerebral blood flow and cognitive function, but requires further investigation.

Previous studies assessing the effects of physical activity breaks on prefrontal cortex activation are limited and inconsistent, mainly due to differing study designs and measurement techniques of cerebral blood flow and cognition. Most earlier studies assessed cerebral blood flow mainly as alterations in blood flow velocity of the middle cerebral artery using transcranial Doppler ultrasound (Carter et al., 2018; Perdomo et al., 2019; Wheeler et al., 2019; Maasakkers et al., 2020), which disregards region-specific and cognitive-task-related changes in the cerebral hemodynamic response, thus eliminating the ability to localize changes in cortical activation. Findings from these studies on more global changes in cerebral blood flow velocity were highly discordant with increases observed in healthy desk workers (Carter et al., 2018), decreases in middle-aged adults with hypertension (Perdomo et al., 2019) and older adults (Wheeler et al., 2019), and no changes in older adults (Maasakkers et al., 2020).

Functional near-infrared spectroscopy (fNIRS) is another portable and non-invasive technique, but with the ability to measure regional task-related cerebral blood flow changes at the cortical level with high temporal resolution (Herold et al., 2018; Pinti et al., 2020). Specifically, fNIRS monitors changes in oxygenated- (Oxy-Hb) and deoxygenated-hemoglobin (d-Oxy-Hb), and is based on the theory of neurovascular coupling. This theory postulates that increased neural demands elicit a corresponding increase in oxygen delivery to meet local energy requirements (Herold et al., 2018). The fNIRS measure of changes in Oxy-Hb has been found to significantly correlate with prefrontal cerebral task-related changes in functional magnetic resonance imaging (fMRI) blood-oxygen-level dependent signals (Sato et al., 2013). Furthermore, fNIRS has a high tolerance to motion artifacts, is of low cost, and is suitable for use in different populations and settings (Herold et al., 2018). These additional advantages can allow for advanced study into the underlying physiological effects of physical activity breaks on prefrontal cortex activation during a working memory task. Yet, fNIRS has not been previously employed in this capacity.

In addition, working memory is an important cognitive function for everyday performance, but inhibitory control has been more prominent in previous studies (Pontifex et al., 2019). Working memory is an important component of the executive functions, encompassing a wide variety of higher-level processes that requires storage and manipulation of information to meet task goals in a short period of time (Baddeley and Hitch, 1994). Studies on region-specific, task-related changes in Oxy-Hb can better elucidate the underlying mechanisms explaining the effects of physical activity breaks on working memory.

Furthermore, the ability to regulate cerebrovascular blood flow from the changing diameter of the vessels is likely to depend on arterial stiffness (Tarumi et al., 2013). Central arterial stiffness has been reported to be lower in well-trained adults compared with their sedentary counterparts (Tanaka et al., 2000).

However, whether variation in arterial stiffness can moderate the effects of cortical activation from frequent, short physical activity breaks, is yet to be investigated. Acute exercise and frequent, short bouts of physical activity during prolonged sitting have also been recognized as beneficial for psychological outcomes among young active as well as middle-aged overweight and obese participants (Wennberg et al., 2016; Niedermeier et al., 2020). It is, unknown whether breaking up sitting with short physical activity breaks would also benefit psychological outcomes in healthy middle-aged adults. We designed this study to understand more of how physical activity breaks in prolonged sitting might affect task-related prefrontal cortex activation as a possible mechanism underlying effects on cognition and mental state.

The primary research question of this study was:

1. What are the effects of uninterrupted sitting and frequent, short activity breaks during 3-h of sitting on activity related changes in prefrontal cortex activation measured as Oxy-Hb?

Our secondary questions were:

2. What are the effects of uninterrupted sitting and frequent, short activity breaks during 3-h of sitting on:
    a. Cognitive performance,
    b. Psychological factors (stress, mood, alertness, and sleepiness), and
    c. Post-prandial blood glucose?
3. Does vascular health (arterial stiffness) moderate the effects of activity breaks on Oxy-Hb?

MATERIALS AND METHODS

Design

We conducted a three-condition randomized crossover experimental study. All study procedures took place at the Swedish School of Sport and Health Sciences (GIH) in Stockholm, Sweden. A full description of the study procedures can be found in the protocol paper (Heiland et al., 2020). This trial has obtained ethical approval by the Swedish Ethical Review Authority, Stockholm, Sweden (Dnr 2019-00998). This trial was registered at www.clinicaltrials.gov (NCT04137211) on October 23, 2019, after recruitment began on May 13, 2019. Data collection was completed on March 13, 2020.

Participants

Adults aged between 40 and 60 years and with a body mass index <35 kg/m^2 were recruited. Those diagnosed with diabetes, epilepsy, heart failure, stroke, or myocardial infarction, or were receiving current treatment for high blood pressure, sleep disorders, depression, or psychosis, were excluded.

Familiarization Session

Participants attended an initial visit to the GIH Laboratory that included collecting demographic data, fitness testing (an incremental treadmill test) (see **Supplementary Material**), providing general health information (questionnaires), being acquainted with experimental procedures, and practicing of the cognitive tests. At the end of this visit, participants were assigned the random order for their conditions. Randomization blinded to the study staff was not possible in this type of study design, but not considered to affect the outcomes. Demographic data included were age, sex, height, weight, and head circumference (to determine the optimal fNIRS cap size).

Pre-condition Monitoring

Time spent in physical activity and sleep during the 24 h period prior to each condition, was measured subjectively through standardized diaries and objectively *via* worn activity monitors (physical activity: hip-worn actiGraph GT3X+ and activPAL micro; sleep: wrist-worn actiGraph GT3X+).

Dietary intake for the 24 h prior to each condition was recorded in a standardized food diary and closely matched across each pre-condition day. Blood glucose monitors were worn during the 24 h prior to, and during each experimental condition, with checks performed upon arrival at the laboratory, after the standardized breakfast, and at the end of the 3-h intervention.

Experimental Conditions

The three experimental conditions, which took place at the same time each visit, and had a minimum 4-day washout between each condition, were: (A) 3-h uninterrupted sitting with 3-min social breaks every 30 min (SOCIAL); (B) 3-h sitting with 3-min bouts of moderate-intensity walking on a treadmill every 30 min (WALK); and (C) 3-h sitting with 3-min bouts of simple resistance activities every 30 min (SRA) [see **Figure 1** in the protocol article (Heiland et al., 2020)]. The SOCIAL break (condition A) consisted of a 3-min chat between a research staff and the participant. The WALK break (condition B) was performed at moderate intensity [75–80% of maximal heart rate (Heiland et al., 2020)]. The SRA break (condition C), involved following a standardized video with light body weight exercises (i.e., three rounds of seven half-squats, nine calf raises, six alternating knee raises with gluteal contractions after each knee raise). While sitting, participants were permitted to read a book and drink water, but not allowed to use any technological devices. They were also encouraged to perform the same activity while sitting at each visit. At 135 min into the experimental condition, participants were offered a toilet break.

On the morning of testing, participants provided four saliva samples (for cortisol testing) – immediately after waking and at 30, 45, and 60 min thereafter. Upon arrival at the laboratory, pre-condition outcome measures were collected, followed by an individually standardized breakfast.

Sample Size

As published in the protocol article (Heiland et al., 2020), effect sizes from previous studies (Hyodo et al., 2012; Endo et al., 2013; Byun et al., 2014; Bediz et al., 2016; Carter et al., 2018; Kujach et al., 2018; Ichinose et al., 2020) using G*Power software (Franz Faul, Universität Kiel, Germany, v 3.1.9.2) were calculated using a *post hoc*, two-tailed, T-test of mean differences

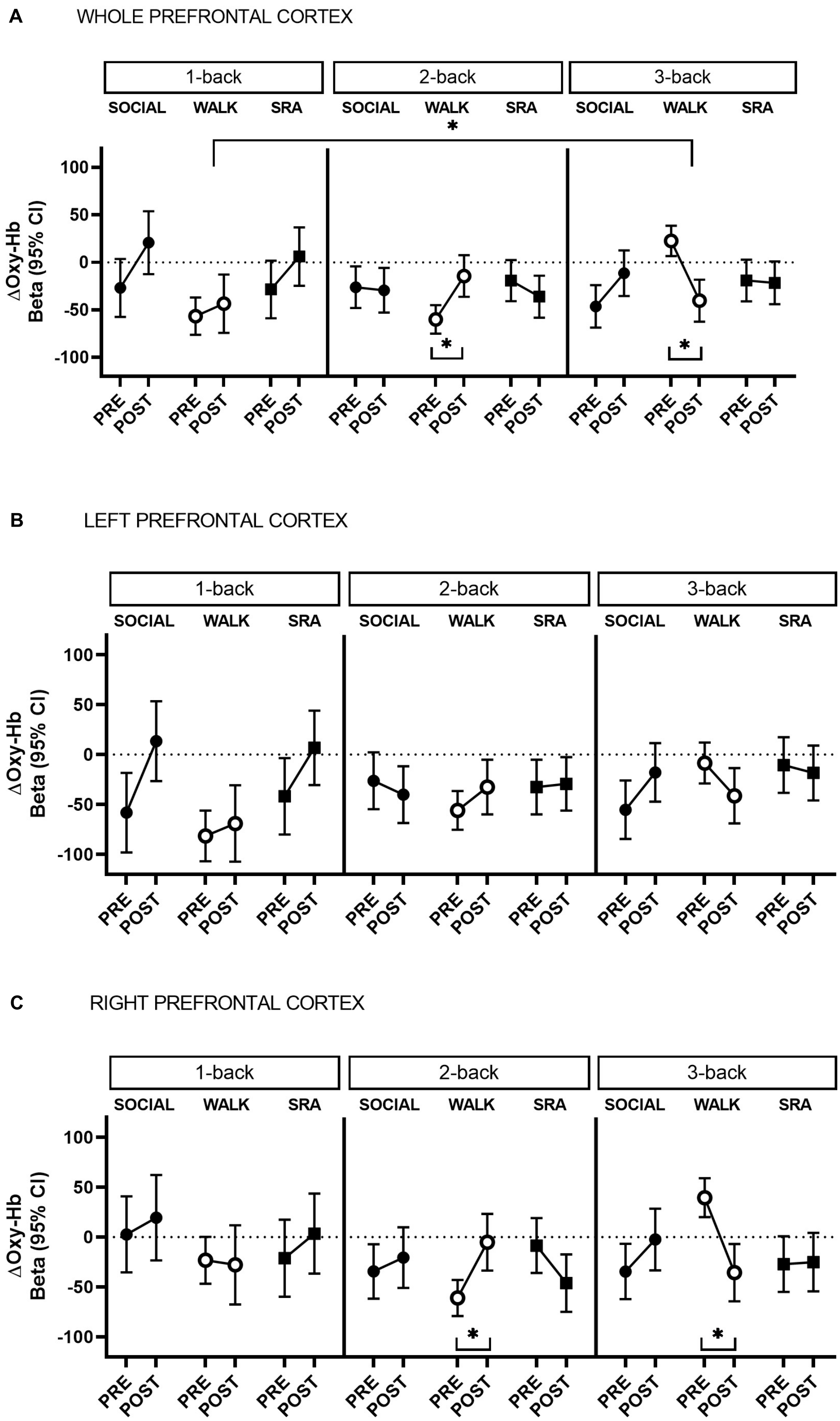

FIGURE 1 | Change in oxygenated hemoglobin (Oxy-Hb) during 1-back, 2-back, and 3-back cognitive tasks from pre-test to post-test, in the whole prefrontal cortex **(A)** and separated by left **(B)** and right **(C)** hemisphere. CI, confidence interval; SOCIAL, social break condition; WALK, walking break condition; SRA, simple resistance activity break condition. *Significant differences within conditions or compared to the baseline (1-back), q-values $\leq$ 0.05 (FDR-adjusted p-values for multiple comparisons).

of matched pairs. Results showed effect sizes between 0.9 and 2.4 for changes in Oxy-Hb. In a subsequent *a priori* analysis using the aforementioned effect sizes, sample sizes calculated ranged between 6 and 13 individuals with an $\alpha = 0.05$ and $\beta = 0.8$ assuming a two-tailed test. Thirteen subjects were chosen based on the largest sample size.

Outcome Measures

Outcome measures were collected immediately prior to, and immediately after each experimental condition.

Oxygenated Hemoglobin

Changes in prefrontal Oxy-Hb and d-Oxy-Hb during working memory tasks (1-, 2-, and 3-back tests) were measured using a multi-channel continuous wave functional near-infrared spectroscopy (fNIRS) instrument (portable NIRSport, 8-8 system), with short-separation channels (NIRx Medizintechnik GmbH, Berlin, Germany). Using the NIRx NIRScap, the optodes were positioned over the prefrontal cortex according to the predefined montage with a standard layout. The NIRScap layout for the prefrontal cortex has eight LED light sources and seven detectors placed according to the standard 10–20 system, offering an ensured source-detector separation distance of 3 cm (**Supplementary Figure 1**). One additional detector was split into eight short-separation detectors placed at a distance of 0.8 cm from each source, to capture superficial blood flow. The cap was placed about 2 cm above the nasion, with the nasion in line with the Fpz position on the cap. A marker was placed below the bottom margin of the cap on the forehead to increase accuracy in repeated replacement of the cap during test days. System calibration was performed before each assessment using NIRStar 15.2 software, and using the predefined montage; and the fNIRS signals were visually quality checked during data collection for motion artifacts. Data were sampled at 7.81 Hz at wavelengths 750 and 820 nm. Changes in Oxy-Hb concentrations were the primary outcome, because it has been shown to be most correlated with regional cerebral blood flow changes (Hoshi et al., 2001). Deoxygenated-hemoglobin concentration changes are reported in **Supplementary Material**. Further details about system calibration and data processing are found in the protocol article (Heiland et al., 2020).

Cognitive Performance

Cognitive performance in working memory was assessed using computerized, numerical N-back tests (1-, 2-, and 3-back tests), administered simultaneously with fNIRS measures (**Supplementary Figure 2**). Initially, each participant was required to stare at a white dot on a black screen for 60 s. Prior to each N-back test, a 40-s practice session with feedback was performed followed by 25 s of rest while staring at the white dot on the screen. Participants were required to indicate (*via* a key press within 2 s from stimulus onset) whether the digit presented on the screen was the same digit as the digit presented 1 stimulus previously (1-back), 2 stimuli previously (2-back), or 3 stimuli previously (3-back). Each digit was presented for 1.5 s at an interstimulus interval of 500 ms. The N-back tests were created using E-Prime 2.0 (Psychology Software Tools, Inc., Pittsburgh, PA, United States). Practice tests were performed at the familiarization session and prior to data collection on each experimental day to reduce learning effects. The outcome variables for cognitive performance included average reaction time (ms) and accuracy (average number of correct responses) for each test across 2 blocks of 20 digit sequences (1-back) or 4 blocks of 20 digit sequences (2- and 3-back). Between each block, instructions were reiterated on the screen until the participant decided to proceed to the next block.

Other Measures

Arterial stiffness, defined as the augmentation index (AIx), was measured using SphygmoCor Technology (Nelson et al., 2010; Butlin and Qasem, 2017). After 5 min of supine rest, high fidelity pressure waveforms were recorded (three times). Estimates with an operator index $\geq 75\%$ were averaged to determine the AIx in percentage, and then dichotomized based on the median split to categorize as low ($<23.5\%$) or high ($\geq 23.5\%$).

Stress was measured using salivary cortisol concentrations using ELISA kit Abcam, ab154996, after being centrifuged at 4 C, at 2800 rpm, for 10 min, and then frozen at −80 C. Three of the saliva samples were used for analysis in this study – the morning sample (immediately after waking up), and pre- and post-intervention testing samples. Additionally, psychological outcomes, including mood [Positive and Negative Affect Scale (PANAS)] (Crawford and Henry, 2004); alertness [10-cm visual analogue scale (VAS)] (Monk, 1989); and sleepiness (Karolinska Sleepiness Scale Questionnaire) (Putilov and Donskaya, 2013) were assessed pre- and post-experimental conditions. Blood glucose was collected continuously, and the area under the curve (AUC) determined during the 3-h intervention period.

Statistical Analysis

fNIRS Data Processing and Analysis

Signals from fNIRS were pre-processed and analyzed using the MATLAB (R2020a, MathWorks, Inc., United States) based software NIRS Brain AnalyzIR Toolbox (Santosa et al., 2018).[1] Raw voltage data were converted to optical density, followed by estimation of relative changes in hemoglobin state concentrations according to the modified Beer–Lambert law and a partial path-length factor (PPF) of 0.1 (PPF = differential path-length factor/partial volume correction = 5/50 = 0.1). First-level statistics involved examining the evoked signal between each source-detector pair using a general linear model (GLM) with a design matrix constructed for the convolution of the stimulus timing and duration (35 s) with a canonical hemodynamic response function, peaking at 6 s. To correct for motion or systemic physiological confounders an autoregressive pre-whitening approach using iteratively reweighted least-squares (AR-IRLS) (Barker et al., 2013) was employed within the GLM including short-separation channel regressors (Santosa et al., 2020), with no other correction applied to minimize manipulation of the data as suggested by Santosa et al. (2018). This has been deemed the best approach (Santosa et al., 2020). Regression coefficients (betas) and error covariances were solved

[1] https://github.com/huppertt/nirs-toolbox

for in the GLM for each channel in each participant, at each condition, at pre-test and post-test to test statistical differences during each cognitive task in each condition, and between conditions (2- and 3-back) and baseline (1-back), in the subject-level statistics. The estimated betas and error covariances in the subject-level statistics for each channel were subsequently used at the group-level statistics.

The group-level statistical models were performed using linear mixed-effects models with condition and time as fixed effects and subject as a random effect to assess within condition differences in the changes in Oxy-Hb (ΔOxy-Hb) from pre- to post-test, averaged over the prefrontal cortex, and separated by right and left hemisphere. The estimated betas from the subject-level analysis from the 1-back, 2-back, and 3-back were employed in the models, and used to test contrasts (baseline vs. 2-back; and baseline vs. 3-back). Time (post–pre) and condition (SOCIAL, WALK, and SRA) interactions were used to estimate intervention effects (between conditions) in the linear mixed-effects models.

A task-based baseline was chosen with minimum arousal for enhanced comparability. The AR-IRLS approach was also chosen to address the issue of serially correlated errors and heavy-tailed noise distributions in fNIRS data (Huppert, 2016). This has been suggested to be the best approach to control for type-I errors in the fNIRS model due to serial correlation (Barker et al., 2013). A false discovery rate (FDR) correction using a Benjamini–Hochberg procedure was used to correct for multiple comparisons, with a critical level of significance set at FDR-adjusted $p \leq 0.05$ (denoted as q-value). Type II power was also reported (Santosa et al., 2018).

Analysis of Secondary Outcomes

The modifying effect of baseline arterial stiffness on changes in Oxy-Hb was assessed in additional stratified linear mixed-effects models in the NIRS Brain AnalyzIR Toolbox software using arterial stiffness as a dichotomized variable based on the median split, because of its skewed nature.

For the other secondary outcomes (i.e., cognitive performance, psychological factors, and AUC of glucose), linear mixed-effects models were performed in Stata version 15 (StataCorp, College Station, TX, United States), using subject as a random effect, to investigate within-person changes from pre- to post-test, and time-by-condition interactions to test intervention effects. Linear mixed-effects models, with subject as random effect were also performed to assess within-subject baseline differences. Statistical significance level was set at $p \leq 0.05$.

RESULTS

Fifteen people were recruited to the study, but two could not complete all three visits. Overall baseline characteristics of the 13 participants can be found in **Table 1**, and by condition in **Table 2**, including accelerometer-derived physical activity and sleep behaviors the day/night before each condition, and differences between conditions. The accelerometer results showed that the time spent sedentary was significantly higher on the day before the WALK condition compared with the day before the SOCIAL condition. In addition, significantly less time was spent in light physical activity on the day before the WALK condition compared with the days before the SOCIAL and SRA conditions.

TABLE 1 | Means and standard deviations (SD) for baseline characteristics of participants.

	All (*n* = 13)
Age, years	50.5 (4.6)
Men, *n* (%)	8 (61.5)
Weight, kg	76.5 (12.8)
Height, m	1.8 (7.3)
Body mass index, kg/m^2	24.0 (2.4)
Cardiorespiratory fitness, mL/min/kg	46.1 (5.4)

Primary Outcome: Changes in Oxygenated Hemoglobin

During the 2-back in the WALK condition there was a significant increase in Oxy-Hb from pre-test to post-test [Beta 45.7 (95% CI 19.6, 71.8), q-value 0.01, Power = 0.82] (**Figure 1A**). This was not significantly different from the 1-back (baseline) during the WALK condition (**Supplementary Table 1**). In contrast, there was a decrease in Oxy-Hb during the 3-back test in the WALK condition [Beta −62.9 (95% CI −89.8, −36.0), q-value 0.001, Power = 0.98] (**Figure 1A**), which was significantly different from the baseline (**Supplementary Table 1**). There were no significant time-by-condition interactions, suggesting that the within condition changes in Oxy-Hb comparing the 2-back and 3-back to the baseline did not differ between conditions.

The within condition changes from pre-test to post-test demonstrated a lateralization. Specifically, the increase in Oxy-Hb during the 2-back in the WALK condition and the decrease in the 3-back were statistically significant only in the right prefrontal cortex [2-back: Beta 55.8 (95% CI 22.8, 88.8), q-value 0.02, Power = 0.80; 3-back: Beta −75.2 (95% CI −109.1, −41.2), q-value 0.001, Power = 0.97] [**Figure 1B** (left) and C (right) and **Supplementary Table 2**]. In comparison to the baseline in the WALK condition, the decrease in Oxy-Hb in the 3-back showed right hemispheric dominance, but became non-significant after correction for multiple comparisons [Beta −70.6 (95% CI −126.5, −14.8), q-value 0.08, Power = 0.50] (**Supplementary Table 1**).

Secondary Outcome: Moderating Effect of Arterial Stiffness on Oxygenated Hemoglobin

After stratifying by arterial stiffness, across the whole prefrontal cortex, there was a significant increase from pre-test to post-test in Oxy-Hb in those with high arterial stiffness during the 1-back SOCIAL [Beta 71.7 (95% CI 15.4, 127.9), q-value 0.04, Power = 0.50; **Supplementary Table 3**] and 2-back in the WALK condition [Beta 42.2 (95% CI 11.4, 73.0), q-value 0.04, Power = 0.60; **Supplementary Table 4**], and a decrease during the 3-back in the WALK condition [Beta −55.0 (95% CI −86.9,

TABLE 2 | Baseline participant characteristics by condition, and accelerometer-derived physical activity and sleep behaviors the day/night before each condition, and differences between conditions (*n* = 13).

	Mean or median (SD or IQR)			Beta-coefficient (95% confidence interval)		
	SOCIAL	**WALK**	**SRA**	**WALK-SOCIAL**	**SRA-SOCIAL**	**WALK-SRA**
Mean lying systolic blood pressure (SD), mmHg	121.8 (12.6)	119.1 (11.7)	122.9 (13.7)	−2.5 (−6.7, 1.8)	1.2 (−3.1, 5.4)	−3.6 (−7.9, 0.6)
Mean lying diastolic blood pressure (SD), mmHg	74.5 (9.1)	72.2 (9.4)	76.5 (10.2)	−2.4 (−5.8, 1.1)	1.9 (−1.5, 5.4)	−4.3 (−7.8, −0.8)*
Mean morning cortisol (SD), ng/ml	6.6 (2.2)	6.8 (3.7)	4.8 (1.8)	0.3 (−1.2, 1.8)	−1.7 (−3.2, −0.2)*	2.0 (0.6, 3.4)*
Median augmentation index (IQR), %	22.2 (15.4)	25.8 (12.8)	23.6 (12.7)	3.7 (−8.0, 7.3)	−0.3 (−1.3, 3.7)	0.5 (−5.3, 3.7)
Mean heart rate (SD), beats per minute	51.3 (8.0)	51.8 (7.0)	51.2 (8.4)	0.5 (−1.4, 2.5)	−0.1 (−2.0, 1.9)	0.6 (−1.3, 2.5)
Accelerometer results from day/night before each condition						
	Mean (standard deviation)			**Beta-coefficient (95% confidence interval)**		
Total time of sedentary bouts, min	146.6 (67.0)	235.9 (252.7)	141.4 (89.0)	88.6 (−29.1, 206.3)	−7.0 (−121.8, 107.8)	95.6 (−15.9, 207.1)
% in sedentary	52.1 (9.0)	61.0 (14.5)	56.0 (11.9)	8.5 (1.1, 15.8)*	2.8 (−4.3, 9.9)	5.6 (−1.2, 12.5)
% in light	40.3 (9.0)	32.3 (13.0)	38.7 (10.5)	−8.0 (−13.5, −2.5)*	−1.0 (−6.3, 4.4)	−7.1 (−12.2, −1.9)*
% in moderate	7.3 (2.9)	6.2 (5.2)	5.0 (3.5)	−0.7 (−3.3, 2.0)	−1.9 (−4.5, 0.7)	1.2 (−1.3, 3.7)
% in vigorous	0.3 (0.5)	0.4 (0.6)	0.3 (0.5)	0.1 (−0.2, 0.5)	0.1 (−0.3, 0.4)	0.1 (−0.2, 0.4)
% in MVPA	7.6 (2.9)	6.6 (5.7)	5.3 (3.8)	−0.5 (−3.4, 2.4)	−1.8 (−4.7, 1.0)	1.3 (−1.4, 4.0)
Step counts	9620 (2258)	8537 (4958)	7883 (3914)	−849 (−3666, 1969)	−1426 (−4172, 1321)	577 (−2088, 3242)
Sleep duration, h	7.1 (0.6)	7.2 (0.7)	7.2 (0.8)	0.1 (−0.4, 0.6)	0.1 (−0.4, 0.6)	−0.03 (−0.5, 0.5)

SOCIAL, social break condition; WALK, walking break condition; SRA, simple resistance activity break condition; MVPA, moderate-to-vigorous physical activity; SD, standard deviation; IQR, Interquartile range.

Missing 1 in WALK and SOCIAL for Augmentation index due to operator index < 75%; Missing 2 in SOCIAL and 1 in WALK and SRA for morning cortisol. Missing 3 in SOCIAL, 2 in WALK, and 1 in SRA from accelerometer results.

**Significant difference ($p \leq 0.05$) between conditions.*

−23.2), *q*-value 0.01, Power = 0.81; **Supplementary Table 5**]. Among those with low arterial stiffness, in the WALK condition, there was an increase in Oxy-Hb during the 1-back [Beta 79.1 (95% CI 18.2, 140.0), *q*-value 0.04, Power = 0.52; **Supplementary Table 3**] and 2-back [Beta 92.0 (95% CI 48.6, 135.5), *q*-value 0.002, Power = 0.95; **Supplementary Table 4**], and a decrease in 3-back [Beta −82.0 (95% CI −126.5, −37.5), *q*-value 0.01, Power = 0.87; **Supplementary Table 5**]. In addition, in the SRA condition there was a decrease in Oxy-Hb during the 2-back in those with low arterial stiffness [Beta −57.5 (95% CI −102.5, −12.4), *q*-value 0.04, Power = 0.50; **Supplementary Table 4**].

In neither the right or left prefrontal cortex were there any significant changes in Oxy-Hb among those with high arterial stiffness (**Figure 2A**). However, right-lateralized prefrontal cortex activity was observed in those with low arterial stiffness during the 2-back in the WALK condition (**Figure 2B** and **Supplementary Table 4**), such that the increase in Oxy-Hb was significant only in the right prefrontal cortex [Beta 114.0 (95% CI 58.4, 169.5), *q*-value 0.01, Power = 0.94]. There was no suggestion of lateralization in the other conditions, except during the 3-back in the WALK condition (**Figure 2B** and **Supplementary Table 5**), there was an indication of a decrease in Oxy-Hb predominantly in the right prefrontal cortex among those with low arterial stiffness [Beta −89.8 (95% CI −146.9, −32.8), *q*-value 0.06, Power = 0.72]. The decrease during the 3-back in the WALK condition was significantly different from baseline, but only in those with low arterial stiffness across the whole prefrontal cortex [Beta −161.1 (95% CI −235.4, −86.8), *q*-value 0.001, Power = 0.96], with a similar decrease in both the left [Beta −166.0 (95% CI −257.3, −74.6), *q*-value 0.01, Power = 0.86] and right prefrontal cortex [Beta −146.8, (95% CI −242.1, −51.5), *q*-value 0.03, Power = 0.70]. There was a significant time-by-condition interaction for the 3-back vs. baseline in those with low arterial stiffness, with no lateralization effects, such that the decrease in Oxy-Hb during the 3-back vs. baseline was significantly different from the SOCIAL condition where there was a non-significant increase in Oxy-Hb.

Secondary Outcomes: Effects on Cognitive Performance, Psychological Factors, and Post-prandial Glucose

After the WALK condition, 3-back reaction time was faster, but no change was observed in accuracy (**Table 3**), and there were no significant time-by-condition interaction effects. For the psychological variables, a significant time-by-condition effect was seen between the WALK and SOCIAL conditions for positive affects. There was a significant increase in positive affects after the WALK condition compared with the SOCIAL condition. There were no significant effects of the interventions on negative affects, nor on the measure of sleepiness. There was a statistically significant increase in alertness after the WALK condition, and there was a time-by-condition interaction between the WALK and SOCIAL conditions. There were significant within condition changes in cortisol levels for all three conditions; and significant time-by-condition effects, demonstrating greater decreases in cortisol after the SOCIAL compared with the WALK and SRA conditions (**Table 3**). Post-prandial glucose

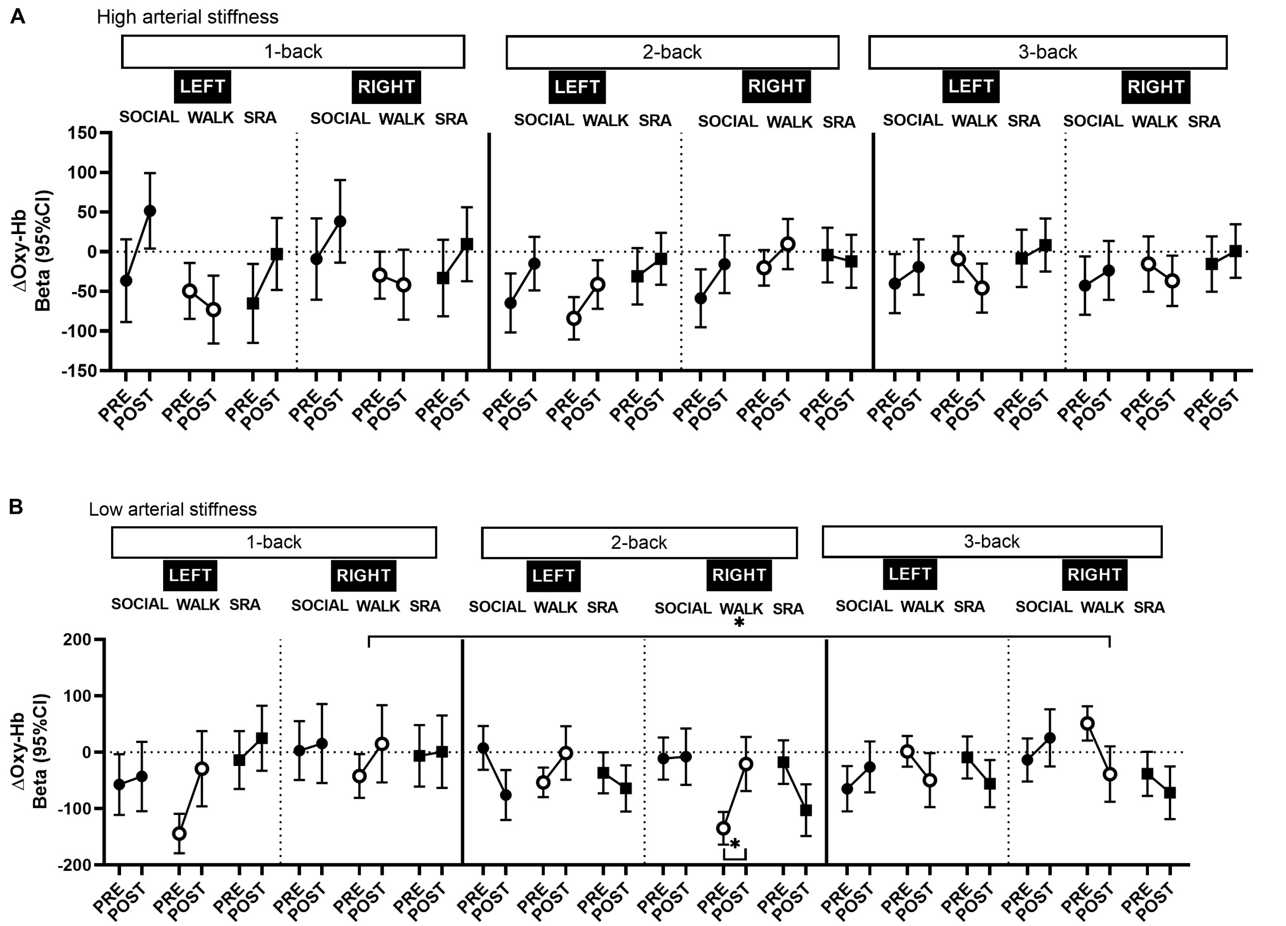

FIGURE 2 | Changes in oxygenated hemoglobin (Oxy-Hb) in the left and right prefrontal cortex among those with **(A)** high arterial stiffness (n = 7) and **(B)** low arterial stiffness (n = 6), during the 1-back, 2-back, and 3-back tasks from pre-test to post-test. CI, confidence interval; SOCIAL, social break condition; WALK, walking break condition; SRA, simple resistance activity break condition. *Significant differences within conditions or compared to the baseline (1-back), q-values ≤ 0.05 (FDR-adjusted p-values for multiple comparisons).

levels (**Supplementary Table 6**) during the interventions did not differ between the conditions, nor were there time-by-condition interaction effects.

DISCUSSION

This randomized crossover study of middle-aged adults found that interrupting extended periods of sitting with frequent, short walking breaks decreased cognitive task-related right prefrontal cortex activation (as measured by Oxy-Hb) during a high workload working memory task. Corresponding improvements on some aspects of working memory performance and psychological factors were also demonstrated from the walking intervention. However, the change in working memory did not differ between the interventions. These findings suggest that frequent, short physical activity breaks during a prolonged day of sitting may to some extent administer positive effects on cognitive performance, while task-related increases in prefrontal cortex activation may not be a predominant underpinning mechanism by which this occurs. Specifically, during the high mental workload task (3-back test), decreases in right prefrontal cortex activation were seen after the walking break condition, yet with a coinciding enhancement in reaction time. However, the changes in prefrontal cortex activation after the walking condition were not significantly different from the other conditions. After stratifying by arterial stiffness, the decrease in prefrontal cortex activation during the 3-back was more pronounced in those with low arterial stiffness across the whole prefrontal cortex. This was significantly different from the prolonged sitting condition. Alertness and mood also improved after the walking breaks compared with the sitting condition. Decreases in stress were significantly greater after the sitting condition compared with both the physical activity conditions.

Physical Activity Breaks and Prefrontal Cortex Oxygenated Hemoglobin

Decreases in prefrontal cortex activation induced by acute exercise are not unexpected and can indicate neural efficiency.

TABLE 3 | Mean and standard deviation (SD) at pre- and post-test for each condition; and beta-coefficient for changes within conditions and time-by-condition interactions.

	Conditions						Change within conditions (Post minus Pre)			Change in post-pre between conditions		
	Pre-test			Post-test			SOCIAL	WALK	SRA	WALK-SOCIAL	SRA-SOCIAL	WALK-SRA
	SOCIAL	WALK	SRA	SOCIAL	WALK	SRA	Beta	Beta	Beta	Beta	Beta	Beta
Cognitive function												
1-back ACC (score)	39.0 (2.5)	39.2 (1.2)	38.7 (2.1)	39.2 (1.1)	39.2 (1.2)	39.4 (1.0)	0.2	0.1	0.7	−0.1	0.5	−0.6
1-back RT (ms)	551.9 (64.3)	567.6 (95.7)	576.7 (104.3)	562.1 (98.0)	565.1 (95.0)	584.7 (97.2)	10.2	−2.5	8.0	−12.7	−2.2	−10.5
2-back ACC (score)	75.0 (6.6)	76.9 (3.2)	75.2 (5.0)	76.8 (3.3)	76.2 (2.7)	76.0 (3.9)	1.8	−0.8	0.8	−2.6	−1.1	−1.5
2-back RT (ms)	605.5 (105.2)	594.3 (101.9)	618.8 (104.2)	611.2 (104.0)	585.4 (106.9)	624.0 (115.7)	5.6	−8.9	5.2	−14.5	−0.5	−14.0
3-back ACC (score)	68.9 (6.4)	69.3 (5.9)	68.8 (9.1)	68.2 (6.3)	68.3 (7.8)	67.8 (7.7)	−0.7	−1.0	−1.1	−0.3	−0.4	0.1
3-back RT (ms)	702.9 (98.3)	707.7 (106.8)	703.2 (120.8)	712.5 (100.1)	670.4 (118.8)	700.3 (122.0)	9.6	−37.3*	−2.9	−46.9	−12.5	−34.4
Positive affects (score)	31.2 (6.6)	28.1 (7.1)	29.7 (6.7)	28.0 (7.1)	31.2 (8.4)	28.8 (7.6)	−3.2	3.1	−0.8	6.2*	2.3	3.9
Negative affects (score)	12.0 (2.3)	12.9 (3.9)	11.4 (2.3)	11.8 (2.1)	11.6 (2.7)	11.2 (1.7)	−0.2	−1.3	−0.8	−1.1	−0.1	−1.0
KSS-sleepiness (score)	4.5 (2.1)	4.9 (1.9)	4.4 (1.9)	4.9 (1.7)	3.9 (1.8)	4.2 (1.5)	0.4	−1.0	−0.2	−1.4	−0.5	−0.8
Alertness (cm)	5.4 (2.3)	4.7 (2.6)	5.3 (2.4)	4.9 (2.4)	6.4 (2.5)	5.7 (2.6)	−0.5	1.7**	−0.2	2.2*	0.8	1.4
Stress (cortisol ng/ml)	7.2 (3.5)	4.8 (2.1)	4.6 (2.1)	3.2 (1.8)	3.2 (2.8)	2.8 (2.0)	−4.0**	−1.6*	−1.7**	2.5*	2.3*	0.2

SOCIAL, social break condition; WALK, walking break condition; SRA, simple resistance activity break condition; ACC, accuracy; RT, reaction time; Positive and negative affects taken from the PANAS questionnaire; Alertness ranges from 0 "not at all" to 10 "completely alert" (highest) cm; KSS, Karolinska sleepiness questionnaire, ranges from 1 "extremely alert" to 9 "very sleepy, great effort to keep awake, fighting sleep."
$^{*}p \leq 0.05$; $^{**}p \leq 0.001$.

Two previous studies using fNIRS reported decreases in prefrontal cortex activation, with coinciding improvements on prefrontal-related cognitive performance, although using different cognitive tasks (Murata et al., 2015; Moriarty et al., 2019). Inconsistencies in the direction of the Oxy-Hb changes used to infer cortical activation across fNIRS studies can be attributed to differences in study designs and processing procedures applied to the data. Some studies of a similar experimental design to the present one, examining physical activity breaks during prolonged sitting, have reported decreases in cerebral blood flow velocity in the middle cerebral artery compared with uninterrupted prolonged sitting (Perdomo et al., 2019; Wheeler et al., 2019). fMRI studies have also demonstrated this effect in randomized controlled trials (RCTs) of longer and shorter physical activity training among middle-aged and older adults (Maass et al., 2015; Coetsee and Terblanche, 2017; Olivo et al., 2021). A recent RCT of older adults found reduced gray matter cerebral blood flow in the frontal region with coinciding improvements on the N-back test after acute exercise compared with those who only rested (Olivo et al., 2021). Neubauer and Fink (2009) explain the theory of neural efficiency as persons having the ability to adapt to higher cognitive processing with a decreased cortical activation after the cessation of exercise. In this case, the brain is better at managing more difficult cognitive tasks with less blood flow, indicating an improved efficiency. A potential anticipatory effect may have led to enhanced cortical activation at pre-test in the WALK condition as indicated by significantly higher sedentary time the day prior, nevertheless the physical activity breaks were able to mitigate the negative circumstances resulting in an improvement on the 3-back task performance at post-test. Thus, physical activity breaks may have led to a decreased requirement for Oxy-Hb during the 3-back task. Support for the neural efficiency theory may also be evident in the results on hemispheric differences, where the decreases in Oxy-Hb were significant only in the right hemisphere. Post-exercise cortical activation normally has a left dominance. Therefore, redistribution of the blood may have occurred leading to less Oxy-Hb demand in the right hemisphere after the walking breaks in order to complete the high workload cognitive task. Young adults have been observed to have a predominate left hemisphere lateralization measured with fNIRS, after exercise during a cognitive task, whereas older adults have no lateralization effects (Yanagisawa et al., 2010; Vermeij et al., 2012; Byun et al., 2014). However, since the present study is a healthy middle-aged population a prefrontal compensatory lateralization mechanism may have transpired.

Moreover, there was a significant increase in activation during the WALK from pre-test to post-test during the 2-back, although not significantly different from the baseline. This high activation may explain the subsequent decrease in cortical activation during the 3-back as there may not have been adequate rest time between blocks to allow the hemodynamic response to go back to resting values. Additionally, the lack of randomization in the N-back test order could have increased anticipatory effects. Nevertheless, improvements in reaction time during the 3-back test were still observed signifying an effect of the walking breaks.

The moderating effect of arterial stiffness further elucidates the mechanistic effects of cerebral oxygenation. The positive effects of physical activity breaks on cognition may be more pronounced in people with better vascular health. Enhanced cardiovascular fitness is associated with reduced arterial stiffness (Goldberg et al., 2012) and can impact the structure and function of the brain (Colcombe and Kramer, 2003; Colcombe et al., 2006). Participants with superior aerobic fitness may therefore be more physiologically adept to manage the demands of the physical activity bouts and thus gain more cognitively (Pontifex et al., 2019). Interestingly, some studies have shown reduced frontal-parietal activation (measured using fMRI) during a high load working memory task, with decreases observed in the right prefrontal cortex, after 5 weeks of training in both younger and older adults compared with controls (Brehmer et al., 2014). Although this study had a longer duration of training than the current study, similar training-induced efficiency effects in brain processing could have occurred as the population in the present study was highly fit. Indeed, in an exploratory analysis we found that 3-back reaction time performance was significantly improved in those with low arterial stiffness during the WALK condition (**Supplementary Figure 3**).

Similarly, a previous study of young adults also showed no effects of frequent, short resistance types of breaks on cognitive function (Charlett et al., 2021). Contrarily, resistance exercises have been beneficial for glucose control and blood pressure acutely, however, in persons with diabetes (Dempsey et al., 2016a,b). SRA breaks were also found in a study of inactive office workers to acutely improve neuroplasticity, using transcranial magnetic stimulation (Bojsen-Møller et al., 2020). Thus, the lack of an effect in the present study may be due to the participants being generally healthy.

The differences in results between the previous research and our results should also be considered in light of the use of short-separation channels during the fNIRS measurement. This approach, in conjunction with advanced statistical methods, has been demonstrated to be the most accurate approach in dealing with physiological confounders (Santosa et al., 2020), but has not been used in this type of study design previously and should be considered in future studies.

Cognitive Function

Other studies that have measured cognitive function after frequent, short physical activity breaks compared with prolonged, uninterrupted sitting, have shown beneficial effects on reaction time in young adult women (Chrismas et al., 2019), but not in overweight/obese middle-aged adults (Wennberg et al., 2016). In our study, participants improved their reaction time but not their accuracy during the 3-back test after the WALK condition. Reaction time has been suggested to be more responsive to physical activity than accuracy (McMorris et al., 2011), due to acute increases in catecholamines (e.g., norepinephrine) after exercise (McMorris et al., 2011; da Silva de Vargas et al., 2017).

Conflicting results with previous research findings may also be due to the moderating effects of timing, duration, and intensity of the physical activity, as well as the timing and type of cognitive test employed after the intervention (Chang et al., 2012). While our study investigated cognitive effects of different types of breaks, further investigations are needed to elucidate how durable the effects are.

Furthermore, employing the N-back test in the current study additionally allowed for testing different mental workloads. No effect was observed in the 2-back test in the present study, which may result from the test not being sufficiently difficult. Indeed discrimination is best when the degree of difficulty is most distinct, such as from the high demanding 3-back test, as seen in a study by Herff et al. (2014) of young adults, and in the present study. However, there have been minimal investigations previously performed looking into the effects of short bouts of exercise on various cognitive workloads. One study in older adults found no effect of acute exercise on either the 1-, 2-, or 3-back tests (Olivo et al., 2021), although a decrease in performance was exhibited with increasing load. There was, nonetheless, an indication of improvement only on the 3-back test for the exercise group compared with the resting group (Olivo et al., 2021). Furthermore, another study of older adults saw improvements on the 2-back test 15-min post exercise cessation (Stute et al., 2020). It is suggested that low intensity exercise may produce immediate positive effects on cognition, whereas higher intensities may have a delayed effect (Chang et al., 2012). Although there is a general idea that exercise produces beneficial effects on cognitive performance, this has mainly been observed in persons with cognitive impairment and dependent on the type of cognitive test measured (Chang et al., 2012). Immediate improvements have been observed from a 10-min bout of moderate exercise on executive function tests of inhibition, such as the Stroop test, in both younger and older adults, with also increases in Oxy-Hb (Yanagisawa et al., 2010; Hyodo et al., 2012). However, the physiological differences from increasing task demands requires further study. It is believed that cognitive load may affect both behavioral and hemodynamic responses differently in younger and older adults, and high fitness may compensate for declines from greater task demand and age (Agbangla et al., 2019). This may be the case in the current study's middle-aged population, where effects from the walking breaks were observed only among those with low arterial stiffness. Thus, not only timing, duration, and intensity of the physical activity need to be taken into consideration, but also age of the population, and the load and type of the cognitive task in relation to behavioral and hemodynamic responses.

Psychological Outcomes

Acute exercise has previously been found to elicit positive effects on perceived attention and mood, compared with those who were sedentary for 2 h (Niedermeier et al., 2020). Even though low intensity physical activity breaks and even less intense shoulder and neck exercise breaks positively impacted subjective sleepiness in sleep restricted adults (Sallinen et al., 2008; Vincent et al., 2018), we did not see any effect of the physical activity breaks on sleepiness. In fact, our participants had adequate sleep prior to test days (see **Table 2**).

Decreases in cortisol levels, denoting stress, was observed after all conditions, but with the greatest changes after the SOCIAL condition. Physical activity breaks may incite a stress reaction that, at moderate levels, elevates attention. Another study found no difference in salivary cortisol levels after sitting uninterrupted for 180 min compared with sitting with physical activity breaks (Sperlich et al., 2018). Salivary cortisol can indicate circulating cortisol from training stress and psycho-physiological stress reactions to exercise, activating the hypothalamic-pituitary-adrenal axis (Wang et al., 2019). Therefore, it is not surprising that the reduction in cortisol is largest after sitting. Post-prandial glucose levels were not significantly different between the conditions, as similarly observed in previous studies (Hansen et al., 2016; Sperlich et al., 2018). This was expected as the participants were relatively healthy.

Other Potential Mechanisms

Increases in catecholamines (e.g., norepinephrine) (McMorris et al., 2011; da Silva de Vargas et al., 2017) or neurotrophic factors may have also influenced the results, although not measured in the present study. Neurotrophic factors are known to increase after acute bouts of exercise and positively impact cognitive function (Nilsson et al., 2020). Specifically, increases in serum brain-derived neurotrophic factor has been observed after conditions of interrupted sitting with frequent, short physical activity breaks compared with uninterrupted sitting, in conjunction with improvements in working memory (Wheeler et al., 2020). In addition, increases in lactate may also explain the improvements in cognitive performance from acute exercise. One study showed that after both a bout of moderate-intensity exercise and high intensity interval exercise there were increases in blood lactate levels, which the authors explained as a potential reason for the improvements on a test of executive function (Tsukamoto et al., 2016). Thus, lactate may replace glucose as the main energy source after acute exercise in order to help in the maintenance of cognitive performance.

Strengths and Limitations

Strengths of our study include registration of our trial and publication of the protocol to add rigor to the analyses and findings. In addition, the use of short-separation channels in combination with a robust statistical approach ideally dealt with systemic contamination and motion artifacts, which augmented the accuracy of the results. Limitations include that mind wandering or other sources of arousal could have occurred during recovery periods of the N-back test, which may have induced changes in Oxy-Hb. This may also be a result of inadequate resting periods between blocks of the N-back, prohibiting the hemodynamic response to go back to baseline levels. Additionally, a lack of pseudo-randomization of N-back tests may have induced anticipatory effects (Yücel et al., 2021). Future experimental designs should take this into consideration. Repositioning of the cap during test days may have also led to slight misplacement of the optodes from pretest to posttest; however, the use of a marker on the forehead helped in maintaining accuracy in cap placement as best as possible. Since we only investigated the prefrontal cortex, activity-related changes in other regions cannot be excluded. Our study was powered to detect between-condition differences in Oxy-Hb, but was less sensitive to changes in cognitive performance. Consequently, more investigations are necessary to assess cognitive effects. Even though the power calculation generated the sample size used in this study, the calculation was based off studies with slightly different experimental designs, thus more studies should be employed with a similar approach to confirm the results and if larger sample sizes are needed. The participants in our study were relatively fit and healthy. Therefore, our findings might not be applicable to populations that are more vulnerable. The finding that arterial stiffness moderates the cerebrovascular response, stresses the need for future investigations to specifically target individuals with high arterial stiffness. Finally, although the inclusion of a control group may be considered more advantageous in order to eliminate bias, the crossover design with randomly ordered, yet counter balanced sessions, alternatively, permitted participants to serve as their own controls and thus, hold constant any variation between individuals.

CONCLUSION

Interrupting prolonged sitting, with frequent, short walking breaks decreased task-related right prefrontal cortex activation as measured by Oxy-Hb during a high load working memory task. Still, frequent, short walking breaks also enhanced working memory performance, suggesting that physical activity breaks during prolonged sitting may help preserve or even improve neural efficiency. Of further importance, alertness and positive mood were enhanced by frequent, short walking breaks compared with prolonged sitting. While more experimental scrutiny is needed to clarify the physiological mechanisms underlying such improved neural efficiency, frequent, short walking breaks may be recommended in middle-aged adults to support psychological well-being during extended periods of sitting and cognitive performance on mentally demanding tasks.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of ethical restrictions. Requests to access the datasets should be directed to MK, maria.ekblom@gih.se.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Swedish Ethical Review Authority, Stockholm, Sweden (Dnr 2019-00998). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EH, ÖE, OT, MF, CE, and ME: conceptualization, methodology, and writing – review and editing. EH, ÖE, OT, MF, and ME: data curation and investigation. EH, ÖE, and OT: formal analysis. ME and ÖE: funding acquisition and project administration. ÖE, CE, and ME: supervision. EH, OT, and ME: validation. EH, OT, and CE: visualization. EH: roles/writing – original draft. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2021.719509/full#supplementary-material

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Sport Practice, Fluid Reasoning, and Soft Skills in 10- to 18-Year-Olds

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Engaging in physical activity and sports has been associated with various cognitive abilities and other personal characteristics. The contemporary link between doing sports and personal attributes such as soft skills and an individual's cognitive abilities have yet to be investigated, however. This study aims to analyze the association between years of practicing a sport, cognitive abilities (in terms of fluid reasoning), and personal attributes (in terms of soft skills). A large sample of 1,115 individuals (10–18 years old) completed the Cattell test (measuring fluid reasoning) and answered a questionnaire measuring six soft skills (adaptability, curiosity, initiative, leadership, perseverance, and social awareness). A multivariate regression analysis show that, after controlling for age and gender, participants' years of practicing a sport were positively associated with three soft skills (i.e., initiative, leadership, and perseverance) and with fluid reasoning. No differences emerged between team and individual sport practitioners. Our findings suggest an association between practicing sports, which entails more than just physical activity, and both cognitive abilities (fluid reasoning) and other important personal characteristics, such as soft skills.

Keywords: sport practice, soft skills, physical activity, cognitive abilities, fluid reasoning

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INTRODUCTION

Physical activity and sports are fundamentally important in late childhood and adolescence, their benefits affecting various aspects of an individual's life, and their mental and physical health. That is why international organizations support them and recommend that people aim for (or maintain) adequate and healthy levels of physical activity and engage in sports (World Health Organization., 2019). Researchers are also paying more and more attention to how engaging in physical activity and sports is associated with other domains, such as academic performance (St Clair-Thompson and Gathercole, 2006), or with positive aging (Salas-Gomez et al., 2020). For older children and adolescents, doing sports may also have other important benefits. It has been found related to cognitive abilities (perception, attention, visuospatial abilities, intelligence; Voss et al., 2010; Voyer and Jansen, 2017; Scharfen and Memmert, 2019) and individual characteristics such as personality and soft skills (Zaff et al., 2003; Khasanzyanova, 2017; de Prada Creo et al., 2020; Feraco et al., 2022). The latter association might be particularly important at a malleable age, such as adolescence, when an individual's cognition and personality take shape (Paus, 2005; Steinberg, 2005; Heckman, 2011; Thompson et al., 2019). Results of studies sustaining the hypothesis of a correlation between sports or physical activity and cognitive abilities or soft skills are mixed (Carson et al., 2016; Li et al., 2017; Salas-Gomez et al., 2020), however, making it difficult to precisely estimate the strength of this association.

Cognitive abilities [which include the abilities involved in mentally handling information (Carroll, 1993)], and soft skills [or the personal qualities that positively regulate emotions, thoughts, and goal-directed behaviors (Park et al., 2004; Robles, 2012)] are fundamentally important to an individual's wellbeing and success in adulthood (McClelland, 1973; Sternberg, 1997; Bertua et al., 2005; Strenze, 2007; Heckman and Kautz, 2012; Bruna et al., 2019). They are also essential in adolescence, as school students rely on these skills for their academic achievement (Lounsbury et al., 2009; Roth et al., 2015; MacCann et al., 2020; Feraco et al., 2021b). Importantly, cognitive abilities and soft skills are thought to be malleable, as suggested by specific interventions (Durlak et al., 2011; Jaeggi et al., 2011; Shipstead et al., 2012; Hodzic et al., 2018; Schutte and Malouff, 2019). Identifying which practical and ecological activities correlate with better cognitive abilities and soft skills could consequently be hugely important, and sports might be a good candidate (Gomez-Pinilla and Hillman, 2013; Carson et al., 2016; Voyer and Jansen, 2017; Bidzan-Bluma and Lipowska, 2018; Hernández-Mendo et al., 2019).

Previous studies found that expert practitioners of various sports had stronger cognitive abilities, in terms of their visuospatial abilities, attention, processing speed, executive functions, or general cognitive abilities (Voss et al., 2010; Moreau et al., 2011; Heppe et al., 2016; Scharfen and Memmert, 2019; Feraco et al., 2021a; Meneghetti et al., 2021). Meta-analyses examining the link between sports and cognitive abilities found only small-to-medium effect sizes, however, and noted small sample sizes, multiple testing approaches, and a low statistical power as major shortcomings of most of the research conducted in this field (Voss et al., 2010; Voyer and Jansen, 2017; Scharfen and Memmert, 2019). Such limitations may lead to the magnitude of the effects being exaggerated (Button et al., 2013; Gelman and Carlin, 2014). Any effect would also presumably be even smaller in populations of non-elite or non-expert sports practitioners, like the majority of adolescents who engage in sports. Our first aim here is therefore to examine the association between sports and cognitive abilities in a large group of preadolescents and adolescents after calculating the sample size needed to detect small effect sizes (r = 0.15; Scharfen and Memmert, 2019). We focus on fluid reasoning as a valid proxy for general cognitive abilities (the g factor), as it has been shown to correlate similarly with the various subcomponents of the g factor during adolescence (Breit et al., 2019).

Then, to add to the literature on the beneficial effects of sports, a second aim is to test the association between a structured and continuous engagement in a sport and the sphere of soft skills. This set of malleable, positive characteristics should influence an individual's wellbeing and success in life by regulating their thoughts, behaviors, and emotions (Robles, 2012; Feraco et al., 2021b). For the purposes of the present study, we consider the six soft skills included in the World Economic Forum model (World Economic Forum., 2016) because of their importance to wellbeing, education, and job success: adaptability, curiosity, leadership, initiative, perseverance, and social awareness. Despite the attention being paid to soft skills around the world (Cinque, 2016; European Commission, 2016; Ministry of Education University and Research [MIUR], 2018; World Economic Forum, 2020), research on the link between sports and soft skills is scarce, and warrants specific studies. It is important to establish whether such an association exists, and whether it is worth promoting sports in adolescents as a way to sustain their soft skills. The few studies conducted to date support the hypothesis that people practicing sports or other extracurricular activities report better soft skills (Zaff et al., 2003; Holt et al., 2013; Arat et al., 2014; Khasanzyanova, 2017; Mızrak et al., 2017; de Prada Creo et al., 2020; Feraco et al., 2022). Practicing a sport is not just a matter of physical and motor abilities. It also demands that people continuously face challenges relating to many difficult situations and interpersonal relationships, and work on their identity and personal qualities to succeed in what they are doing (Eccles, 1999; Clark et al., 2015; Fakhretdinova et al., 2020). Practicing a sport has been found associated with students' leadership (Holt et al., 2013; Clark et al., 2015; de Prada Creo et al., 2020), perseverance (Fourie and Potgieter, 2001; Guillén and Laborde, 2014), and emotional intelligence (Laborde et al., 2017), but also with other soft skills, such as initiative, adaptability, and curiosity (Feraco et al., 2021b, 2022).

To sum up, the aim of the present study is to investigate the cross-sectional association between years of practicing a sport and both cognitive abilities (in terms of fluid reasoning) and personal characteristics (in terms of soft skills) in a large sample of 10- to 18-year-olds. This age group was chosen because both cognitive abilities and personality are malleable at this time of life (Steinberg, 2005; Heckman, 2011), and because few studies have tested these hypotheses in adolescents. We hypothesize that years of practicing a sport should correlate positively: with fluid reasoning, given that expert sportspeople perform better than non-experts in various cognitive tasks (Voss et al., 2010; Voyer and Jansen, 2017); and with soft skills because practicing a sport also involves a host of relational and personal competences (Guillén and Laborde, 2014; de Prada Creo et al., 2020; Feraco et al., 2021b). We examine whether all six soft skills considered, or some of them in particular (such as leading a team or persevere toward one's aim for long time, will be related) are associated with the practice of a sport. Both types of association (with cognitive abilities and with soft skills) are expected to be small, given the findings of previous meta-analyses and the fact that we analyze yearly increments (Scharfen and Memmert, 2019; Feraco et al., 2021b).

MATERIALS AND METHODS

Participants

The study sample consisted of 1,115 individuals (521 males, M_{age} = 13.51, SD_{age} = 2.16) from 10 to 18 years old (see **Table 1** for the sample's characteristics), who were enrolled on a voluntary basis. Of these individuals, 984 engaged in amateur sports for at least a year (M_{year} = 5.71, SD = 3.68), and the other 131 had never engaged in any sport. The amount of practice was measured in terms of the number of years respondents had engaged in sport during their lives, rated as: 0; 1–2 years; 3–4 years; 5–6 years; 7–8 years; 9–10 years; 11–12 years; or 13–14 years. Respondents also indicated how many hours a week they spent practicing their sport (see **Table 1**), and 436 of them also specified the type of sport they were practicing at the time of data collection.

The sample size needed was calculated using a power analysis. We simulated 10,000 datasets for different sample sizes based on a theoretical covariance matrix in which a small association ($r = 0.15$; Scharfen and Memmert, 2019) between years of sport practice and the seven dependent variables was hypothesized. On each dataset, we ran the analyses described in the section "Results," and calculated how many times all hypothesized associations were contemporary significant ($p < 0.05$). It emerged that 1100 participants sufficed to obtain a power of 0.99.

Materials

All the scales used in the study showed acceptable reliability coefficients, as calculated on the actual sample ($0.64 < \alpha < 0.79$).

Soft Skills

The soft skills questionnaire (Feraco et al., 2021b) measures the six soft skills included in the personal qualities branch of the World Economic Forum. (2016):

Adaptability, or the ability to adapt positively to new and uncertain situations in everyday life (e.g., "I'm scared by situations that are new to me."; Martin et al., 2012);

Curiosity, or the epistemic desire to acquire new knowledge (e.g., "Whenever I see something new, I try to understand what it is."; Berlyne, 1960);

Initiative, or deliberate personal growth referred to general everyday life situations (e.g., "If a decision has to be made, I make it."; Robitschek et al., 2012):

Leadership, or the characteristics typical of leadership, such as being the reference person in a group, or supporting and motivating others (e.g., "I can take the lead in team efforts."; Peterson and Seligman, 2004);

Perseverance, or the general tendency to work hard to reach aims despite difficulties (e.g., "Faced with a difficult situation, I don't give up."; Duckworth et al., 2007);

Social awareness, or sense of responsibility for the community and the environment (e.g., "It's important that all people be treated equally."; Peterson and Seligman, 2004).

Each subscale is composed of six items (except for leadership, with four items) scored on a 6-point Likert scale. Each total is derived from the sum of its corresponding items.

TABLE 1 | Characteristics of the study sample.

Age	10	11	12	13	14	15	16	17	18
Males	43	74	105	76	71	45	53	43	11
Females	38	59	113	89	73	80	70	58	14
Sport practitioners	76	122	187	148	133	110	107	82	19
Total	81	133	218	165	144	125	123	101	25
Hours per week	4.64 (2.77)	4.01 (2.58)	4.14 (3.11)	4.55 (2.99)	5.26 (3.2)	4.64 (3.36)	4.68 (3.16)	4.38 (3.56)	3.76 (3.13)

Number of participants, females, males, sports practitioners (who had engaged in a sport for at least a year), and hours of practice per week, with means and standard deviations (in brackets).

Cognitive Abilities

Culture-Free Intelligence Test (Cattell, 1940). This test measures fluid reasoning with four different time-limited tasks that involve: (i) finding the image that completes a sequence (12 items, 3 min); (ii) finding the image that differs from the others (14 items, 4 min); (iii) finding the image that completes a matrix (12 items, 3 min); and (iv) finding the image that presents the same spatial relationships as a target figure (8 items, 2.5 min). A total score was calculated from the sum of the items correctly answered in all four tasks.

Procedure

We collected data in two phases (520 participants responded between January and March 2019; another 595 responded between January and February 2020, before the COVID-19 pandemic spread). Participants were recruited through schools. In September 2019 and September 2020, we contacted the principals of numerous schools in northern and central Italy. After obtaining their agreement, consent forms were distributed to the parents of potential participants. After receiving the parents' consent, we organized our data collection. Eighteen-year-old participants completed their own consent form.

A trained psychologist collected the data during school time and under the supervision of a class teacher. Participants first completed a personal information section, indicating their age, gender, and engagement in sports. Then they answered the soft skills questionnaire and performed the Cattell test. The order of presentation of the two measures was randomized between classes. For the questionnaire, participants were told there were no right or wrong answers. For each of the four cognitive tasks, they read the instructions and answered the sample items together with the experimenter, who also told them about the time limit, and stopped them when their time was up. The procedure took less than 1 h to complete in each class.

RESULTS

All analyses were run using the "lavaan" package in R (Merkle and Rosseel, 2018; R core team., 2020). A multivariate regression analysis was used to study the effect of practicing a sport (years) on the levels of soft skills (adaptability, curiosity, leadership, perseverance, and social awareness) and cognitive abilities (fluid reasoning). The dependent variables (soft skills and fluid reasoning), but not the years of sport, were scaled ($M = 0$; SD = 1) to make the results comparable and easier to interpret. Age and gender were always added as covariates to control for their effect on the dependent variables (Gur et al., 2012; Voyer et al., 2017; Heintz et al., 2019).

The results of the multivariate regression model show that the years of practicing a sport correlated with four of the seven dependent variables considered, after accounting for the effect of age and gender (see **Figure 1**). We found that the number of years spent practicing a sport correlated positively with initiative ($p < 0.001$; $\beta = 0.06$), leadership ($p < 0.001$; $\beta = 0.08$), perseverance ($p < 0.001$; $\beta = 0.06$), and fluid reasoning ($p < 0.01$; $\beta = 0.04$), but not with adaptability ($p > 0.05$; $\beta = -0.00$), curiosity

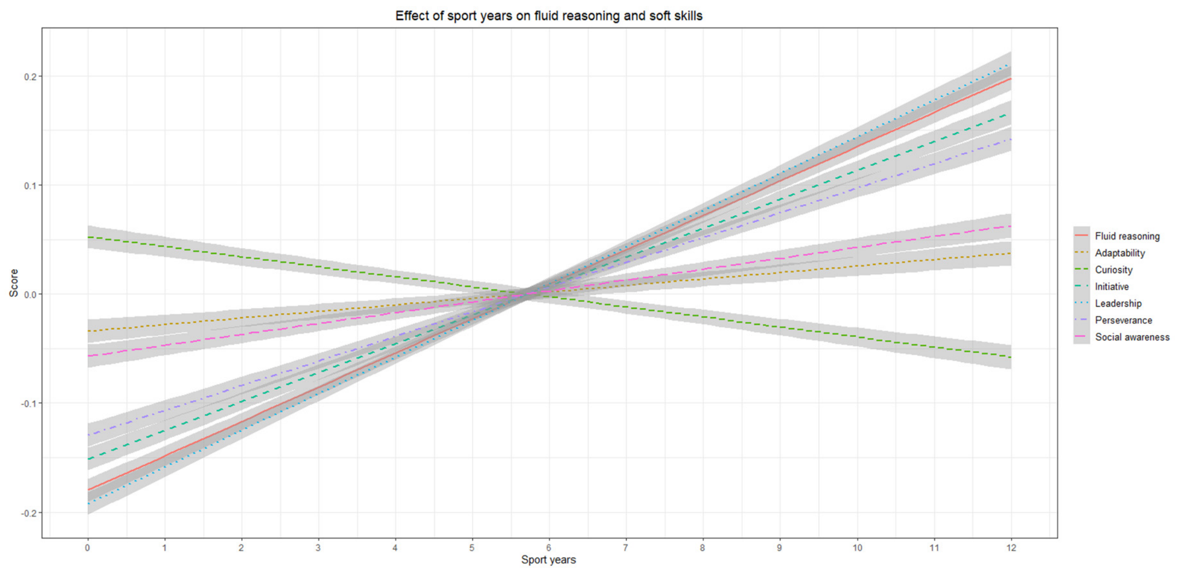

FIGURE 1 | Association between number of years of practicing a sport, soft skills, and fluid reasoning. 15% confidence intervals are shown for readability. Soft skills and fluid reasoning are scaled to mean = 0; SD = 1.

($p > 0.05$; $\beta = -0.01$), or social awareness ($p > 0.05$; $\beta = 0.02$), with beta estimates indicating the amount of standardized increase for every 2 years. Descriptively, as concerns the covariates: age was positively associated with fluid reasoning, and negatively associated with all the soft skills except adaptability and social awareness, which remained stable with age; gender differences only emerged for adaptability (in favor of males), and social awareness (in favor of females). See **Table 2** for the complete results including the covariates.

We also checked whether practicing different sports might affect the dependent variables differently by running a second multivariate linear regression model with the type of sport as the predictor, and age and gender as covariates. This was done after dichotomizing the types of sport as team sports (e.g., basketball, handball) and individual sports (e.g., tennis, athletics) (Laborde et al., 2016). Only data for the subsample of participants who provided information about the sports they engaged in and those who reported never engaging in any sport were considered ($N = 567$). The analysis yielded no significant results regarding the type of sport ($p > 0.05$; $\beta \leq |0.05|$).

DISCUSSION

International organizations promote the value of physical activity and sports in the general population (World Health Organization., 2019) because they are good for our physical and mental health, but the literature suggests that they may have other benefits. Practicing sports may also influence our cognitive abilities (e.g., visuospatial skills, attention, perception), and various aspects of our personality or character, such as soft skills (Eccles, 1999), particularly during childhood and adolescence (Paus, 2005; Steinberg, 2005; Heckman, 2011; Thompson et al., 2019). Hence our present effort to further analyze how practicing sports (in terms of the number of years involved) correlates with cognitive abilities and soft skills in 10- to 18-year-olds (an age when these abilities and skills are still malleable). A large sample (1,115 participants) was examined to test the presumably small (as suggested by Scharfen and Memmert, 2019) effects of years of practicing a sport on seven dependent variables (cognitive abilities, adaptability, curiosity, initiative, leadership, perseverance, and social awareness).

The results of our multivariate regression analysis confirmed our hypotheses regarding cognitive abilities and three soft skills, which correlated significantly with the number of years spent practicing a sport. As expected, these correlations were small (ranging from 0.04 for cognitive abilities to 0.07 for leadership), which goes to show the importance of large sample sizes to detect these associations (Voss et al., 2010; Voyer and Jansen, 2017; Scharfen and Memmert, 2019). They nonetheless support the existence of a positive link between years of practicing a sport and important personal characteristics (cognitive abilities and soft skills). Our results also suggest that every additional year of practice counts: for children engaging in sports from early on, at 8 years old, their cognitive abilities would potentially have a 0.20 standardized benefit after 10 years. This is far from negligible, considering that: cognitive abilities are important throughout our lives (Ree et al., 1994; Roth et al., 2015); these sports are usually practiced freely, not as an activity intended to train cognitive abilities; and sports have enormous benefits on other aspect of a child's life (e.g., physical and mental health; World Health Organization., 2019).

The effects of sport on soft skills seems particularly interesting. Our sample of adolescents seemed to identify improvements in their cognitive abilities as they grew older, but a decline in their soft skills (the association between participants' age and soft skills was constantly negative and significant). This might be a problem, given the importance of soft skills in their future lives (Heckman and Kautz, 2012; World Economic Forum, 2020). However, we found that perseverance, leadership, and initiative correlated with years of practicing a sport, in line with previous reports (Fourie and Potgieter, 2001; Holt et al., 2013; Guillén and Laborde, 2014; Clark et al., 2015; de Prada Creo et al., 2020; Feraco et al., 2021b). This might be due to the specific demands of sporting activities. For instance, perseverance might be a core characteristic of sportspeople because it is rare for anyone to see results immediately after a single training session. Learning a new technique or movement might initially be frustrating, and it can only be mastered by staying focused, continuing to practice, and coping with setbacks. At the same time, sports involve competitions that can often last a whole year with unexpected results, and failures need to be adequately managed, avoiding the temptation to give up, in order to achieve good results at the end of the year – and this takes perseverance. People engaging in sports must also constantly take responsibility for their actions and make decisions all the time they are playing, as they know it will affect their own or their team's results. They have to learn to take action that is appropriate and well-timed, so practicing a sport could really empower an individual's personal initiative. There is also a clear association between practicing a sport and developing leadership (de Prada Creo et al., 2020). Whether they engage in individual or team sports, practitioners almost never work by and for themselves. Every action they take has consequences on their own performance, and that of others (teammates, trainers, sponsors), and they must nurture their ability to collaborate with others (planning training sessions, understanding and respecting the role of every member of the group) in order to reach the goals they have set themselves.

TABLE 2 | Results of multivariate regression analysis.

Dependent variable	Predictor	B	*SE*	Z	CI [2.5, 97.5]
Fluid reasoning	Age	0.14***	0.01	1.21	(0.11;0.16)
	Females	0.06	0.06	1.10	(-0.05;0.17)
	Years of practicing sports	0.04**	0.02	2.58	(0.01;0.07)
Adaptability	Age	-0.00	0.01	-0.10	(-0.03;0.03)
	Females	-0.22***	0.06	-3.61	(-0.33; -0.10)
	Years of practicing sports	0.01	0.02	0.74	(-0.02;0.04)
Curiosity	Age	-0.04***	0.01	-3.22	(-0.07; -0.02)
	Females	0.03	0.06	0.53	(-0.09;0.15)
	Years of practicing sports	-0.01	0.02	-0.67	(-0.04;0.02)
Initiative	Age	-0.06***	0.01	-4.48	(-0.09; -0.04)
	Females	0.10	0.06	1.66	(-0.02;0.21)
	Years of practicing sports	0.06***	0.02	3.91	(0.03;0.10)
Leadership	Age	-0.05***	0.01	-3.44	(-0.07; -0.02)
	Females	-0.00	0.06	-0.07	(-0.12;0.11)
	Years of practicing sports	0.07***	0.02	4.64	(0.04;0.11)
Perseverance	Age	-0.08***	0.01	-5.93	(-0.11; -0.06)
	Females	0.09	0.06	1.60	(-0.02;0.21)
	Years of practicing sports	0.06***	0.02	3.66	(0.03;0.09)
Social awareness	Age	-0.02	0.01	-1.62	(-0.05;0.00)
	Females	0.46***	0.06	7.82	(0.34;0.57)
	Years of practicing sports	0.02	0.02	1.49	(-0.01;0.06)

*Dependent variables (fluid reasoning and soft skills) are scaled to mean = 0; SD = 1. **p < 0.01 and ***p < 0.001. SE = standard error; z = test statistic; β = beta coefficient; CI = confidence interval; Females indicates the difference between males and females, with males as the baseline.*

In short, our findings support the claim that practicing sports can nurture people's cognitive abilities and personality (Eccles, 1999). It can strengthen an individual's sense of identity and achievement (Eccles, 1999; Clark et al., 2015). These added values of practicing sports deserve to be better investigated in experimental or longitudinal studies. Some soft skills - adaptability, curiosity, and social awareness - did not reveal any significant associations with years of practicing sports in our sample of adolescents, but further research might be able to shed more light on their role. Importantly, we also found no difference between individuals practicing team versus individual sports in the seven dependent variables considered here: specific research might better investigate this issue.

While the above considerations seem plausible, they are only the fruit of speculation because we adopted a cross-sectional approach that prevents us from drawing any conclusions on the causality of the effects identified. It may be, for instance, that more perseverant people keep practicing sports. A longitudinal approach would be better suited to investigating any improvements in a given individual's cognitive abilities and soft skills. We only administered one test on fluid reasoning as a measure of cognitive abilities, disregarding many other abilities that might be influenced by practicing a sport (e.g., processing speed, perception, attention, visuospatial abilities; Voss et al., 2010; Voyer and Jansen, 2017; Scharfen and Memmert, 2019). We also limited the soft skills considered to six, though there are many others that it would be worth testing. It might be rightly argued, too, that we only considered the number of years our participants had spent practicing a sport, without considering the amount of time they dedicated to it (e.g., hours per week) or the level of expertise they had reached, which might also affect the results (Meneghetti et al., 2021).

CONCLUSION

We analyzed the association between sports, in terms of years of practicing a sport, and seven variables: cognitive abilities (fluid reasoning), and six soft skills. Our findings support the conviction that practicing a sport not only promotes physical and mental health in general but may also be associated with important cognitive abilities (fluid reasoning) and personal characteristics (soft skills). Even if the effects identified were small, preadolescents and adolescents who had been practicing a sport for more years scored higher in terms of their cognitive abilities and three soft skills, i.e., initiative, leadership, and perseverance.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: doi: 10.6084/m9.figshare.17429738.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Padua's Ethics Committee for Research in Psychology. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

TF and CM contributed to the conception and design of the study, wrote sections of the manuscript, revised the manuscript, and read and approved the submitted version. TF performed the statistical analysis, organized the database, and wrote the first draft of the manuscript.

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SYSTEMATIC REVIEW
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The Effects of Combined Cognitive-Physical Interventions on Cognitive Functioning in Healthy Older Adults: A Systematic Review and Multilevel Meta-Analysis

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Research has shown that both physical exercise and cognitive training help to maintain cognition in older adults. The question is whether combined training might produce additive effects when the group comparisons are equated in terms of exercise intensity and modality. We conducted a systematic electronic search in MEDLINE, PsycInfo, and Cochrane Central Register of Controlled Trials (CENTRAL) databases to identify relevant studies published up to February 2021. Seven hundred and eighty-three effect sizes were obtained from 50 published intervention studies, involving 6,164 healthy older adults, and submitted to a three-level meta-analysis. Results showed that combined training produced a small advantage in comparison to single cognitive training on executive functions, whereas both types of training achieved similar effects on attention, memory, language, processing speed, and global cognition. Combined training achieved higher training gains in balance than single physical training, indicating a transfer from cognitive training to balance. Performing cognitive and physical exercise simultaneously, and interactive training (e.g., exergames, square stepping) produced the largest gains in executive functions, speed, and global cognition, as well as the largest improvements in physical functions. Aerobic training was associated with higher effects in attention and fitness, whereas non-aerobic training produced larger effects in global cognition and balance. For all cognitive and physical outcomes, training resulted more advantageous when performed in a social context, even though individual training obtained similar results in balance as group training.

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INTRODUCTION

Highly developed nations are experiencing large increases in the proportion of elderly citizens, due mostly to reduced birth rates and the increased longevity of their inhabitants (Reuter-Lorenz and Park, 2014). Demographic estimations predict that the proportion of the population above 60 will reach 35% by 2050 (Eurostat, 2016). Furthermore, the old-age dependency ratio (people aged 65 and above relative to those aged 15–64) will increase from 29.6% in 2016 to 51.2% in 2070 (European Commission, 2018). As aging affects several key cognitive functions negatively, such as processing speed, working memory, long-term episodic memory, and executive control functions (Baltes and Lindenberger, 1997; Park et al., 2002; Rönnlund et al., 2007), there is considerable interest in finding effective ways to improve and/or maintain these cognitive functions that are central for performing daily living activities.

Several longitudinal and cross-sectional studies conducted during the last two decades have shown that cognitive training interventions (e.g., Ball et al., 2002; Willis et al., 2006; Basak et al., 2008; Anguera et al., 2013; Ballesteros et al., 2014, 2017; Toril et al., 2016), regular physical activity (e.g., Colcombe and Kramer, 2003; Guiney and Machado, 2012; Voelcker-Rehage and Niemann, 2013; Prakash et al., 2015; Muiños and Ballesteros, 2018), and exposure to novelty (Park et al., 2014) can promote and/or maintain cognitive functioning in late adulthood.

A large body of research shows the positive link between physical activity and cognition. For a detailed description of the brain mechanisms associated with physical activity and its effects on cognition (see Kraft, 2012; Ballesteros et al., 2015). These reviews support the view that the combination of physical activity in conjunction to cognitive training may generate synergistic beneficial effects that either one alone.

Physical Training

Physical activity can be defined as any bodily movement produced by skeletal muscles that require energy expenditure. Both moderate- and vigorous-intensity physical activity improve health (World Health Organization, 2019). A large body of research also corroborates the benefits of physical activity on brain structures and functions (Voelcker-Rehage et al., 2010; Erickson et al., 2011; Ruscheweyh et al., 2011; Liu-Ambrose et al., 2012; Bherer et al., 2013), and as a protection against age-related cognitive decline in executive functions and memory (Colcombe and Kramer, 2003; Hötting and Rödder, 2013; Voelcker-Rehage and Niemann, 2013; Bamidis et al., 2014). Aerobic exercise has been specially related to improvements in cognition (e.g., Colcombe and Kramer, 2003; Hindin and Zelinski, 2012), but coordination training (Voelcker-Rehage et al., 2011), resistance training, Tai Chi (Pons Van Dijk et al., 2013; Muiños and Ballesteros, 2015), and dance (Kattenstroth et al., 2013; Zilidou et al., 2018; Esmail et al., 2019; for reviews see Netz, 2019; Muiños and Ballesteros, 2020a,b) produce positive effects on brain and cognition in older adults.

Cognitive Training

Cognitive training refers to a structured intervention that includes tasks designed to improve or maintain the cognitive functions that decline most with age. In the last years, several meta-analyses (Powers et al., 2013; Kelly et al., 2014; Lampit et al., 2014; Toril et al., 2014; Wang et al., 2016; Chiu et al., 2017; Tetlow and Edwards, 2017; Vázquez et al., 2018; Gavelin et al., 2020) examined the effects of cognitive-based training in older adults. Overall, their results indicated that video games and other cognitive-based training programs lead to small to moderate improvements in several aspects of cognition. A systematic overview of systematic reviews (Gavelin et al., 2020) on 46 reviews found a small mean effect of cognitive training in healthy and cognitively impaired older adults. Furthermore, larger effect estimates were related to higher review quality, and the authors concluded that cognitive training seems to improve cognition, but that the scarcity of high-quality evidence and heterogeneity in reported findings do not allow to estimate the clinical value of the effects.

However, other reviews (Gates et al., 2019; Lintern and Boot, 2019) were less optimistic about the effects of cognitive training. If effective, it seems that the transfer effects to untrained cognitive functions are either weak (Simons et al., 2016; Souders et al., 2017) or null when controlling for placebo effects and publication bias (Sala et al., 2018). Furthermore, several of the mentioned meta-analyses on cognitive training included also studies in which the participants also performed physical exercise (e.g., Legault et al., 2011; Maillot et al., 2012; Barnes et al., 2013; Shatil, 2013), confounding the effect of pure cognitive training with a potentially additive effect of cognitive training combined with physical activity.

Combined Physical and Cognitive Training

The concurrent or simultaneous performance of physical exercise and cognitively challenging activities is known as combined, multidomain, or dual task training. Research on dual task performance has a long tradition in investigating how increased attentional demands affect either cognitive or physical performance due to prioritization in resource allocation to one or the other domain. Thus, these paradigms assume that our information processing system is limited and that conflicts in resource allocation are solved via interference control (McIsaac et al., 2015). On the other hand, neuroscientific approaches do not assume that one activity is necessarily executed on behalf of the other, but that combining physical and cognitive training might result in a mutual enhancement of both activities (Hötting and Rödder, 2013).

Animal studies have shown that physical exercise and cognitive stimulation contribute differentially to neuroplasticity in the mice brain, and whereas physical exercise promotes neurogenesis, cognitive stimulation promotes the differentiation of these new cells (Kronenberg et al., 2006; Kempermann et al., 2010). In humans, numerous studies have shown the beneficial effect of physical training on cognitive and functional brain plasticity in older adults, especially in hippocampal areas (Erickson et al., 2009, 2011; Niemann et al., 2014), suggesting similar mechanisms of neurogenesis as in animal models. Regular exercise has also been related to higher brain-derived neurotrophic factor (BDNF), which is involved in neurogenesis, synaptogenesis, and dendritic branching (Ruscheweyh et al., 2011; Håkansson et al., 2017), resulting in increased learning-related plasticity (Hötting and Rödder, 2013; Cassilhas et al., 2016). The release of BDNF serum is higher when physical exercise precedes cognitive training than vice versa (Nilsson et al., 2020), suggesting that physical exercise may have a facilitating effect on cognitive interventions.

A crucial question is whether combined physical and cognitive interventions, as opposed to single cognitive training or single physical training, produce synergistic effects on cognition, i.e., a combined effect that is greater than the effect produced by its components separately (Lustig et al., 2009; Kraft, 2012; Hötting and Rödder, 2013; Bamidis et al., 2014; Ballesteros et al., 2015). A systematic review (Lauenroth et al., 2016) analyzed 20 intervention studies on cognitive and physical combined training. The authors concluded that simultaneous or successive physical exercise and cognitive training were more effective than physical or cognitive exercise interventions alone. However, the results should be treated with caution due to the methodological heterogeneity of the original studies. Another review (Law et al., 2014) included 8 randomized controlled studies (RCT), but only 3 involved cognitively healthy older adults. Despite the small number of studies, the results indicated that participants' cognition in the combined cognitive and physical training condition was better than that of controls.

Meta-Analytic Evidence on Combined Interventions

Several meta-analyses were conducted on the effects of combined interventions on the cognitive functions of older adults. The meta-analysis conducted by Zhu et al. (2016) included 20 interventional controlled trials ($n = 2{,}667$ healthy older adults). The results showed that combined interventions were superior to controls with a small effect size (0.29 random-effects model, $p = 0.001$) and physical exercise alone (overall effect size 0.22, $p < 0.01$), but not to cognitive training.

The meta-analysis of Guo et al. (2020) included 21 RCT conducted with healthy participants and adults with mild cognitive impairment (MCI) ($n = 1{,}665$). Combined interventions and cognitive training alone produced larger effects in executive functions compared to controls (Standardized Mean Difference; SMD = 0.26, $p < 0.01$). Differences were found between the effects produced by combined training and cognitive training alone (SMD = 0.13, $p > 0.05$) or physical training alone (SMD = 0.13, $p > 0.05$).

A network meta-analytic study (Bruderer-Hofstetter et al., 2018) included 11 combined or multi-component RCT studies conducted with healthy older adults ($n = 670$). According to their results, multi-component interventions were more effective than physical exercise and cognitive training alone and improved specific aspects of physical capacity and/or cognitive function. Physical and cognitive training conducted simultaneously or separately in older adults with normal cognition were effective, but in older adults with mild cognitive impairment (MCI), training performed separately was more effective.

On the other hand, the meta-analysis by Gheysen et al. (2018) included 41 intervention studies, 30 of which were conducted with healthy older adults. The authors investigated whether the combination of physical and cognitive interventions led to greater improvement in different cognitive processes compared to physical or cognitive interventions alone, and/or passive and active control groups. Results indicated that combining physical and cognitive training tasks in the same protocol produced larger benefits. Compared to the control condition, combined interventions produced larger cognitive gains ($g = 0.316$; $p < 0.001$). Combined interventions also induced significantly larger gains in cognitive functioning than physical exercise alone ($g = 0.16$; $p = 0.008$). However, combined and cognitive training alone did not differ ($g = 0.02$; $p = 0.836$). Nonetheless, the authors concluded that physical activity programs for older adults produce greater benefits when they incorporate cognitive tasks, and recommended activities such as dance and Tai-Chi that combine physical activity and cognitive training (see Muiños and Ballesteros, 2020a,b).

Vaportzis et al. (2019) included 7 combined physical and cognitive interventions, 25 physical, and 9 cognitive intervention studies in their meta-analysis of real-world interventions with healthy older adults. Five out of the seven combined studies reported superior results in the combined intervention vs. active controls. However, the meta-analysis did not find any significant difference in cognitive outcomes between combined and cognitive interventions alone.

Methodological Questions and Meta-Analytic Inconsistencies

The meta-analyses discussed in the previous section thus produced some conflicting results, especially in terms of effect sizes. The conflicting results might be due to several factors as the heterogeneity of the studies included in each meta-analysis. Moreover, as in the case of the meta-analyses on cognitive training, meta-analytic works on combined cognitive-physical training often merge non-equivalent training interventions. Different study parameters, such as the dosage and the type of physical exercise (e.g., aerobic exercise *vs.* balance training), might modulate the training outcomes differentially. Also, on a within-study level, combined training is often compared with a different type of physical exercise than the one performed in the combined condition. The inclusion of a control condition in the design reduces expectation bias that could inflate training outcomes and account for other threats to internal validity (Gold et al., 2017). However, in contrast to pharmacological interventions, in behavioral studies, it is extremely difficult to find psychological placebos or "sham" interventions, as any activity might have the potential to produce unexpected effects on cognition and behavior. For example, in some studies, the training effect produced by exergames was compared with that produced by balance (Eggenberger et al., 2015; Schättin et al., 2016) or strength training (Bacha et al., 2018). In other studies, aerobic training was compared with stretching plus strength (Barnes et al., 2013), or stretching, strength, and balance training (Ten Brinke et al., 2020). In other cases, both groups received a similar training part, such as aerobic and strength training, and another different one (Boa et al., 2018). Or both groups did not differ in the physical training type or load, but the single physical training group also received cognitively enhancing dual-task training (Kayama et al., 2014). Furthermore, activities used as a control condition in some studies, as balance and/or strength training, were used in other studies as experimental conditions (Hiyamizu et al., 2012; Gschwind et al., 2015; Jehu et al., 2017; Wongcharoen et al., 2017; Laatar et al., 2018), adding a further challenge for meta-analytic analyses. It seems logical to think that aerobic exercise exerts a different effect on body and cognition than, for example, balance or strength training. Hence, the comparison of two groups that receive different training regimes does not allow to isolate the combinatory effect of physical exercise and cognitive training when both groups perform different physical or cognitive activities. Nonetheless, all meta-analyses conducted to date included at least one of the studies mentioned above, computing effect sizes from the comparison of non-equivalent physical training components.

Meta-analyses might also suffer from analytical flaws. Most interventional studies include more than one outcome measure, which produces an interdependency of effect sizes. Traditional univariate approaches often apply the *sample wise* procedure, averaging the dependent effect sizes within studies into a single effect size by computing a weighted average (Cheung, 2019). However, this method underestimates the degree of heterogeneity or the variance of the population and might lead to lower statistical power due to information loss (Cheung, 2019). A relatively novel approach for dealing with the dependency of effect sizes consists in applying a three-level structure to a meta-analytic model (Assink and Wibbelink, 2016). This approach considers three different variance components and allows effect sizes to vary between participants (sampling variance), outcomes (within-sample variance), and studies (between-study variance). The three-level meta-analytic model allows analyzing the training effects on different cognitive functions within the same study (i.e., within-study heterogeneity) and their reliability across different studies (i.e., between-study heterogeneity).

Aims and Hypotheses of This Multilevel Meta-Analysis

The primary aim of this systematic review and three-level meta-analysis was to shed light on whether combined physical and cognitive training is more effective than single-domain training (physical or cognitive alone) in maintaining and/or improving cognition in healthy older adults while controlling for the dependency of effect sizes, and differences in the training protocols. Specifically, the present multilevel meta-analysis addressed the following research questions:

(1) Does combined training produce synergistic or additive effects, i.e., are the effects obtained by the combination of cognitive and physical training larger than those obtained by each of its components separately?
(2) Are the effects of cognitive training differentially modulated when combined with aerobic vs. non-aerobic exercise?
(3) Does simultaneous cognitive and physical training produce better results than sequential training performed on the same day (sequential training schedule) or different days of the week (separate training schedule)?
(4) Does the type of cognitive training (computer, interactive, such as exergames, or multicomponent training) influence the training outcomes?
(5) Does training produce better results when performed in groups than when performed individually?
(6) Finally, to what extent are the results influenced by the quality of the studies, publication bias, year of publication, sample size, age, or training duration?

METHODS

The review was registered in the International Prospective Register of Systematic Reviews (PROSPERO, https://www.crd.york.ac.uk/prospero/; CRD42020175632). To conduct this systematic review and multilevel meta-analysis, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA; www.prisma-statement.org) guidelines for reporting studies (Moher et al., 2009). The objective was to ensure comprehensive and transparent reporting methods and results. The process and methods were established before conducting the review.

Literature Search Strategy

A systematic electronic database search was conducted to identify relevant published studies. The MEDLINE, PsycInfo, and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched to identify relevant studies published up to February 2021, with no period specified for the date of publications.

The search terms were intersections of terms referring to the combination of cognitive and physical activities in older adults intended to improve cognitive and physical health. The search terms were intersections of terms referring to the combination (*combined OR combination OR simultaneous OR dual OR concurrent OR sequential OR multimodal OR multidomain OR multicomponent*) of cognitive *(cognitive OR mental OR memory OR "executive functions" OR "video games")* and physical *(physical OR exercise OR motor OR mobility OR strength OR aerobic OR endurance OR cardiovascular OR kinetic OR kinect OR exergame*)* interventional studies *(training OR program OR intervention OR fitness OR activity)* conducted with older adults *(older OR elderly OR elderlies OR aging or aging OR aged OR seniors).* For the full search strategy (see **Supplementary Material S1**).

Next, the electronic search was complemented by reviewing the reference lists of the retrieved articles and reviews and then hand-searching cited articles considered to be of interest. Titles and abstracts were first screened by two of the authors (JAR and MM), who then individually screened the full text of relevant articles. In the event of disagreement, a consensus was achieved following a discussion with JMR and SB. If the study was relevant for our analysis but the data necessary to calculate the effect sizes were missing, the authors were contacted via email to obtain the relevant data. Of the four datasets requested, two were provided by the authors. The two remaining datasets were not provided by the authors, so we resorted to extracting the data from the graphs provided in the papers using the online tool WebPlotDigitizer version 4.3.

Selection Criteria

We restricted inclusion in this review to research articles written in English and published in peer-reviewed journals. They also had to meet the following criteria:

(A) **Study participants**: Healthy older adults (mean age 60 years or older) with no known cognitive impairment or other mental illness or neurological disorder including depression, stroke, dementia, or Parkinson's disease. Studies involving both healthy and cognitively impaired older adults (with mild cognitive impairment or dementia) were only included if the results for the healthy sample were reported separately. In that case, we only used data from the healthy sample.
(B) **Combined interventions**: The studies included at least one combined physical and cognitive training group.
(C) **Comparison groups**: Studies were considered when they included, in addition to the combined training group, at least one of the following: (a) a single-physical exercise group; (b) a single-cognitive training group; (c) a passive control group (e.g., waiting list, business as usual); (d) an active control group (alternative interventions, such as leisure activities, health education or toning exercises).
(D) **Equivalent training components**: when the comparison groups consisted of single physical and/or single-cognitive training, only those studies in which the training components of the combined and the single-component training were identical (i.e., the same dosage of aerobic exercise, strength, or balance training) were included.
(E) **Study design:** We included only intervention studies with pre/post assessments of cognitive outcomes, excluding single-session trials (e.g., studies with only a post-test assessment). The studies could be randomized controlled trials (RCT), cluster-RCT, or non-RCT.
(F) **Descriptive statistics**: Studies were included if they provided the statistics needed to compute the *g* effect size index and its confidence interval or provided sufficient information to calculate at least one effect size for at least one cognitive outcome measure.
(G) The outcome measures assessed cognitive or physical functions objectively, as described in more detail below.

Data Extraction

Outcome Measures

The cognitive outcomes included objectively assessed cognitive domains of processing speed, attention, memory, executive control, verbal abilities, global cognition, as well as composite scores from test batteries. Processing speed included tests that measured reaction times. Attention included divided, selective, and sustained attention measures. The classification of executive functions assessments was based on published factor analyses (e.g., Miyake et al., 2000; Friedman and Miyake, 2004) and included tests that measured working memory, inhibition, and flexibility. Memory included short- and long-term memory tests. Language included assessments of verbal, categorical, and phonological fluency. Global cognition comprised the results of cognitive screening tools, and lastly, composite scores included z-scores from test batteries.

Objectively assessed physical measures were classified into fitness, strength, and balance. In the case of dual-task paradigms (the simultaneous performance of a physical and a cognitive task), we only computed the scores of the cognitive task, but not the physical scores. Given the close relationship between balance and gait, we coded gait parameters within the balance category, such as stride variability or step length. Results of simple motor reaction time tests were not included.

When authors provided the results of subcategories of screening tools (e.g., MMSE), we only coded the global score within the category "global cognition." Several studies included combined interventions with and without other treatments. In this case, we only computed the combined training group that did not receive other treatments. When a study included additional training groups whose training components differed from those of the combined group, we only computed the data from equivalent groups. When a test was tailor-made or unusual, we analyzed the task paradigm in detail by examining the procedures, item-specific analyses, and online and graphic material. For a detailed description of the tests used in each study (see **Supplemental Material S2**).

Moderators

(a) mode of delivering the combined training (simultaneous, sequential, and separate). Simultaneous training included interactive interventions, such as exergaming (e.g., pedaling and steering a bicycle in a virtual world and attainment of goals), body-mind activities in psychomotor modality, in which the cognitive training is performed while carrying out physical movements, and dual-task interventions, in which cognitive and physical components are typically separate tasks but performed at the same time. Combined interventions in sequential mode included cognitive and physical exercises performed one after the other in the same session. For combined interventions in the separate mode, the two training components were delivered on different days of the week. In square stepping exercise (SSE), the cognitive demands depend on the difficulty of the foot placement patterns being performed and progression through the stepping protocols. At beginner levels, as in Gill et al. (2016), the activity can be conceptualized as a lower extremity coordination exercise and we considered it a physical component. In SSE with increasingly more complex stepping patterns, as in Schoene et al. (2015), the activity can be conceptualized as a visuospatial working memory task requiring a stepping response and considered a simultaneous cognitive-physical intervention; (b) Aerobic *vs.* non-aerobic exercise. The aerobic intensity was classified according to the information provided by the authors. Low aerobic exercises such as walking or light group activities (e.g., catching balls) were classified as non-aerobic. Other moderators were: (c) number of training sessions; (d) intervention length in weeks; (e) minutes of training per week; (f) study quality; (g) mean age and its standard deviation (SD), and (h) year of publication. A couple of studies did not report the precise number, duration, and/or frequency of training sessions, but only minimum and maximum values; in these cases, we coded the mean value of each group.

Assessment of Methodological Quality

Two authors (SB and MM) independently conducted a qualitative assessment of the methodological quality of the studies included in this review using the Standard Quality Assessment Checklist (Kmet et al., 2004). In this checklist tool, the maximum score for study quality is 28. Methodological quality is considered excellent if the score is >80%, good if it is 70–79%, fair if it is 50–69%, and poor if it is <50%. When there was a disagreement in scoring a study, the authors discussed the matter until they reached an agreement. For a detailed description of the quality assessment of the reviewed articles (see **Supplemental Material S3**).

Interrater Reliability

The studies were coded by two independent reviewers (JAR and JMR). Disagreements were solved by discussion. When this process was finished, a third reviewer (MM) randomly selected and coded ten studies from the whole set, and interrater reliability for this subset of studies was calculated. Cohen's Kappa for the categorical variables and intraclass correlations for continuous variables ranged from 0.94 (classification of measured functions) to 1 (research design).

Effect Sizes

To quantify the differential training effect of combined vs. cognitive and/or physical training alone, and/or active/passive control on cognitive and physical outcome measures, we computed the standardized mean differences of effect sizes and their variance for each physical and cognitive outcome of the original papers using the formula

$$g = [c_m]\left[\frac{\left(\bar{y}^{Exp.}_{Post} - \bar{y}^{Exp.}_{Pre}\right) - \left(\bar{y}^{Cont.}_{Post} - \bar{y}^{Cont.}_{Pre}\right)}{S_{pooled}}\right]$$

$$S_{pooled} = \sqrt{\frac{\left(n_{Exp.} - 1\right)\left(S^{Exp.}_{Pre}\right)^2 + \left(n_{Cont.} - 1\right)\left(S^{Cont.}_{Pre}\right)^2}{n_{Exp.} + n_{Cont.} - 2}}$$

$$c_m = \left[1 - \frac{3}{4\left(n_{Exp.} + n_{n_{Cont.}}\right) - 9}\right]$$

where $\bar{y}^{Exp.}_{Post}$ and $\bar{y}^{Exp.}_{Pre}$ are the experimental group posttest and pretest means, $(S^{Exp.}_{Pre})^2$ is the variance of the pretest scores, c_m is a bias correction factor inversely proportional to the sample size, $n_{Exp.}$ is the sample size of the experimental group, and $\bar{y}^{Cont.}_{Post}$, $\bar{y}^{Cont.}_{Pre}$, $(S^{Cont.}_{Pre})^2$, $n_{Cont.}$ are the corresponding values for the comparison group. As we used a bias correction factor, the Standardized Mean Difference (*SMD)* computed was thus Hedge's g instead of Cohen's d. The standard deviation of Hedge's g was computed with the following equation:

$$S_g = \sqrt{c_m^2\left(\frac{n_{Exp.} + n_{Cont.}}{n_{Exp.} \bullet n_{Cont.}}\right)\left(\frac{n_{Exp.} + n_{Cont.} - 2}{n_{Exp.} + n_{Cont.} - 4}\right)\left(1 + \frac{(n_{Exp.} \bullet n_{Cont.})g^2}{n_{Exp.} + n_{Cont.}}\right) - g^2}$$

Each study usually included several dependent variables for the same outcome, either because the experiment produced several dependent variables for the same task (e.g., reaction times (RT), error rates, delayed and immediate recall, etc.), or because different assessment tools were used to evaluate the same function. We computed at least two effect sizes (ES) for each dependent variable reported in the original articles: one for the effect of the combined cognitive-physical treatment, and one for the single-cognitive and/or the single-physical and/or the active and/or passive control group. In all cases, the means and sample sizes for the combined group were the same, and only the means and sample sizes for the three possible comparison groups (cognitive, physical, and control) differed. This indicates that these ES had dependence between them stemming from two sources: several ES were computed from the same original study (for different dependent variables), and they used a common group (the combined group) as a reference point to compute ES.

Statistical Analyses

Modeling ES using a three-level structure is a better approach than a two-level structure when there are several dependent effect sizes in each independent study, but only if the heterogeneity of the sampling variance is substantial. In three-level meta-analytic models, three different sources of variance are modeled: the third level describes the variance of effect sizes between studies (between-study), the second level describes the variance of effect sizes of the experiments, or measurements nested within each study (within-study), and the first level describes the sample variance. We performed the multilevel random-effects analysis with and without moderators using restricted maximum likelihood estimation. This analytical solution was specifically designed to account for the non-independence among ES, and it was the preferred methodology as the sampling variability was not too high.

Heterogeneity among our effect sizes was assessed using the Q statistic. A large Q-value indicates that differences between ES do not derive from a common population mean from the original study samples but are accounted for by other reasons. The Q statistic is distributed as a χ^2 distribution.

Statistical analysis was performed using the rma.mv function of the metaphor package (version 2.4) (Viechtbauer, 2010) within the R software environment (version 4.0.1; R Core Team, 2021). We followed the analytical steps presented by Assink and Wibbelink (2016). Dot-plot figures were depicted using Mathematica (version 10.4) with software developed specifically for this study.

Outlier Analysis

Outliers or influential cases are considered cases that could distort the results in one or another direction. We performed outlier and influential case diagnostics using the *influence* function of the metaphor package. This function calculates the influence of deleting one case at a time on the model fit or the fitted/residual values, based on several indices:

the externally standardized residual, DFFITS value, Cook's distance, covariance ratio, the leave-one-out amount of (residual) heterogeneity, the leave-one-out test statistic of the test for (residual) heterogeneity, and DFBETAS value(s). In one study, the identified influencer cases constituted the only cognitive effect sizes (Norouzi et al., 2019). Regarding the follow-up outcomes, the influence function suggested deleting all cases belonging to one specific study. Given that according to the metafor package description, the chosen cut-offs are (somewhat) arbitrary, and that substantively informed judgment should always be used when examining the influence of each case on the results, we decided not to use this function for the follow-up cases but base our decisions on the visual inspection of funnel plots. **Supplementary Table S4** summarizes the cases that were detected and removed from the database before the meta-analysis.

Publication Bias

Despite our comprehensive review and systematic search strategy, it is possible that some studies were missed due to publication bias. Generally, studies that fail to produce significant results are either not submitted for publication by the authors or rejected by the editors or reviewers. This could lead to bias toward the publication of significant statistical effects, something known as the "file-drawer problem." Although there are many ways to estimate publication bias (Rothstein et al., 2006), most do not apply to multilevel studies due to dependent effect sizes. We addressed this issue with several procedures. First, we visually inspected the funnel plots of cognitive and physical functions. In the funnel plots, effect sizes were charted against the standard error around the estimated summary effect of cognitive and physical ES. An asymmetric funnel plot (e.g., usually an under-representation of non-significant and/or negative effects on the bottom left side of the plot) would suggest the existence of publication bias. To test the statistical significance of the plots, we applied Egger's test (Egger et al., 1997), which analyzes whether the standardized effect sizes can predict study precision (defined as the inverse of the standard error) in a linear regression. Furthermore, we generated fail-safe numbers (i.e., the number of non-significant ES needed to change a significant into a non-significant result) following different approaches (Rosenthal, 1979; Orwin, 1983; Rosenberg, 2005). Finally, we used the trim-and-fill method of Duval and Tweedie (2000a,b) to determine how many ES would need to be imputed to restore the symmetry of the funnel plot.

RESULTS

Search Results

The initial search yielded 6,457 studies. After excluding duplicates and studies that did not meet the inclusion criteria, 50 studies were included in the analysis. **Figure 1** shows the PRISMA flow diagram of the systematic search and study selection.

Descriptive Results: Studies and Participant Characteristics

In most studies, there was more than one outcome measure. After removing 26 outliers (3.21%), our meta-analysis included a total of 783 effect sizes, of which 697 corresponded to pre-post assessments and 86 to pre/follow-up assessments. **Table 1** shows the descriptive data of all the primary studies included in our analysis. The eligible studies were published up to February 2021. The largest number of published studies was in 2015 with 10 studies, followed by 2017, 2020, and 2014 (7, 6, and 5 published studies, respectively). Four studies were published in 2012 and 2018, three in 2012 and 2021, and two in 2009 and 2016. In 2002, 2006, 2011, and 2019 there was just one published study per year. The countries with the largest number of published studies were Japan and USA with six studies each, followed by Germany with five studies, and Switzerland and France with four studies each, Australia and Canada with three studies each, Brazil and Thailand with two studies, and China, Finland, Greece, Iran, Italy, Mexico, Myanmar, Portugal, Singapore, South Korea, Spain, and Tunisia with one study each. Two studies were multisite, participating Italy, Greece, Spain, and Serbia in one, and Spain, Germany, and Australia in the other study. A total of 6,164 healthy older adults participated in the 50 studies with a mean age of 72.12 ($SD = 4.51$) years. Bamidis et al. (2015) did not report the mean age, but their participants were older than 55 years, so the mean age was computed over 50 studies. The number of participants in each study ranged from 13 (You et al., 2009) in a pilot study to 1.190 (Ngandu et al., 2015) with a global mean of 123.928 ($SD = 201.885$). Of all studies, six studies included a follow-up assessment. However, as the total of follow-up outcomes only summed up 86 effect sizes, these were only analyzed in a summary fashion and not by cognitive or physical functions. Twenty-seven studies reported a comparison of combined training *vs.* active or passive control ($n = 4,555$), nine studies compared combined training with single cognitive training ($n = 441$), and 14 studies compared combined training with single physical training (n = 1,168). Two studies included two types of combined training compared with a control group (Wollesen et al., 2017) and single cognitive training (Yu et al., 2021). The combinatory mode for the combined groups was sequential (13 studies, $n = 1,780$), separate (9 studies, $n = 2,760$), or simultaneous (28 studies, $n = 1,624$). The total duration of the intervention ranged from 4 weeks (Wongcharoen et al., 2017; Norouzi et al., 2019) to 144 weeks (Andrieu et al., 2017) with a global mean of the duration of 20.29 weeks ($SD = 26.04$). The total number of training sessions ranged from 8 (Kitazawa et al., 2015) to 745 (Andrieu et al., 2017), with a global mean of 61.9 sessions ($SD = 124.05$). The duration (in minutes) of cognitive intervention sessions ranged from 30 (Schoene et al., 2013; Linde and Alfermann, 2014; van Het Reve and de Bruin, 2014) to 360 (Pieramico et al., 2012; Shah et al., 2014), with a global mean of 114.8 min per week ($SD = 64.46$). The duration of physical intervention sessions ranged from 40 min (Schoene et al., 2013) to 250 (Shah et al., 2014) with a mean duration of 118.31 min ($SD = 49.40$). The studies varied in the type of physical training, and in 38 studies, the training included fitness, and/or balance,

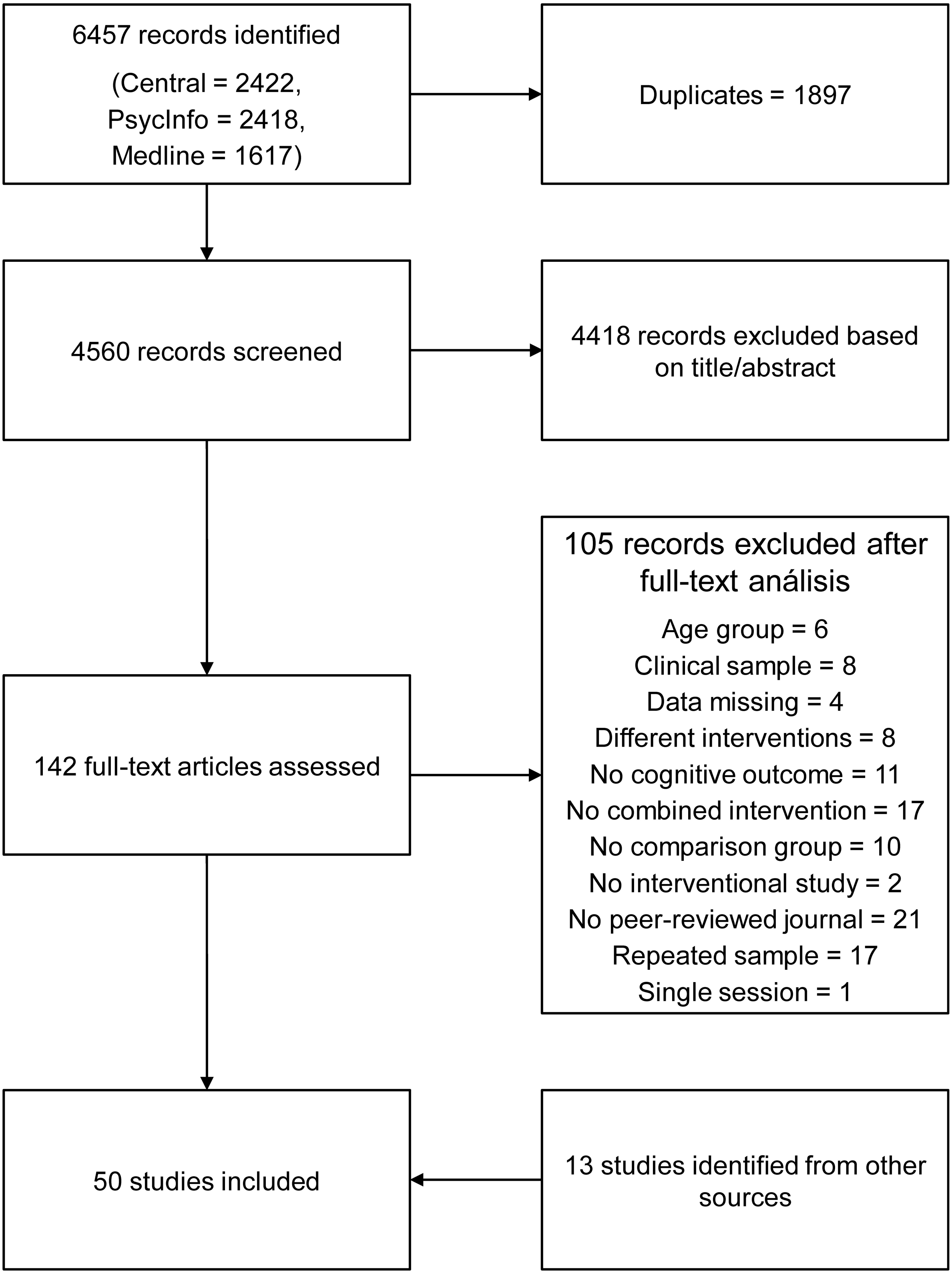

FIGURE 1 | PRISMA flow diagram of the search strategy.

and/or strength. The aerobic exercise intensity was moderate to high in 17 studies ($n = 1,235$) and low to none in 29 ($n = 3,176$) studies. In four studies, it was not possible to determine the aerobic exercise intensity. Cognitive training included a variety of exercises (memory, planning, reasoning, visuospatial skills, attention, switching tasks, arithmetic, verbal fluency, problem-solving, and other cognitive tasks). In 15 studies ($n = 650$) the cognitive training was performed interactively (exergames, psychomotor exercises, and square stepping), in 17 studies ($n = 3,197$) via computer games or computer tasks, and in 18 studies ($n = 2,317$) *via* a multicomponent training (paper-pencil tasks, group games, verbal games, etc.) or verbal exercises.

Outcome measures varied across the studies, with most of the studies assessing several cognitive functions, such as attention, switching, executive functions, processing speed, memory, and global cognition (see **Supplementary Table 5**), as well as physical outcomes, such as strength, endurance, frailty, gait, balance, risk of falls, functional mobility or VO_2max.

Analysis of Bias

A visual inspection of the funnel plot corresponding to cognitive pre-post outcomes [number of effect sizes (k) = 507] revealed asymmetry with larger effect sizes on the right lower side of the plot, which was confirmed by the Egger's regression test ($z = 4.108$, $p < 0.001$, $\beta = -0.024$, 95% *CI* [−0.112, 0.064]). This test is identical to regressing effect sizes on standard errors, where weights are inversely proportional to the variance of effect sizes. In the Egger's test a significant positive intercept means that smaller studies with less precision are associated with larger effects. The trim-and-fill method estimated that to restore symmetry are necessary to add 32 ES to the left side of the plot, which would reduce the estimated summary effect to 0.114 ($p < 0.001$, 95% *CI* [0.083, 0.145]). Even though smaller studies produced the largest effect sizes, the standard errors of effect sizes were represented uniformly in a range from 0.244 to 0.975, suggesting that the underrepresentation of negative results was not only a question of small-study effects (i.e., higher standard errors) but occurred in smaller as well as in larger samples (see **Figure 2A**). The results of the fail-safe tests indicated that it would need 21,678 ES (based on Rosenberg's approach) or 30.933 ES (following Rosenthal's approach) to increase the p-value of an overall ES of 0.145 to above 0.05. According to Owen's approach, 507 ES would be necessary to reduce the average ES from 0.194 to 0.097.

Regarding physical functions ($k = 203$), the funnel plot also suggested an asymmetry skewed to the right. Again, Egger's test was significant ($z = 4.225$, $p < 0.001$, $\beta = 0.017$, 95% *CI* [−0.103, 0.136]), and the trim-and-fill method estimated that 27 ($p < 0.001$, 95% *CI* [0.113, 0.234]) ES should be added to restore the symmetry of the funnel plot, reducing the estimated summary effect to 0.174 (**Figure 2B**). In this case, the imputed effect sizes for the funnel plot to be symmetric were in a lower range of standard errors, indicating that especially negative results from studies with lower precision were needed to restore the symmetry. However, compared to the cognitive outcomes, the main amount of ES was in the middle of the plot, suggesting fewer studies with large samples in physical outcomes than in cognitive outcomes. To reduce the significance of an overall ES of 0.091 to a P level above 0.05, 13,326 ES would be needed taking Rosenthal's approach, or 3,540 ES taking Rosenthal's approach. According to Owen's approach, it would be necessary 203 additional ES to reduce the ES from 0.316 to 0.158.

In the case of cognitive pre/follow-up outcomes ($k = 73$) (**Figure 2C**), we detected no asymmetry, which was confirmed by a non-significant Egger's test ($z = 0.176$, *n.s.*, $\beta = 0.166$, 95% *CI* [0.056, 0.277]). The trim-and-fill method estimated that only one ES ($p < 0.001$, 95% *CI* [0.12, 0.223]) would be necessary to restore the symmetry of the funnel plot. According to Rosenberg, it would need 871 ES, and according to Rosenthal, 970 ES, to increase the P level of an average ES of 0.178 to above 0.05. Orwin's approach estimated that 73 ES would be necessary to add to reduce an average ES of 0.19–0.09.

Regarding physical pre/follow-up outcomes (**Figure 2D**), the results of the bias analysis should be taken with caution because of the reduced dataset ($k = 13$). Egger's test did not detect any asymmetry ($z = 0.117$, *n.s*, $\beta = 0.408$, 95% *CI* [0.212, 0.6]), and the fail-safe calculations indicated that it would be necessary 225 (Rosenberg) or 218 (Rosenthal) ES to reduce the statistical significance of an ES of 0.416 to above 0.05. According to Owen's approach, it would require 13 ES to reduce the estimated ES of 0.427 to 0.214. The trim-and-fill method estimated that no ES had to be added to restore the symmetry (*n.s.*, 95% *CI* [0.309, 0.525]).

Overall Effect Size

Figure 3 displays the summary effect of pre-post cognitive and physical outcomes by study. The estimated summary effect across all studies ($n = 50$) for pre-post comparison of cognitive outcomes ($k = 507$) was $g = 0.22$ ($p < 0.001$, 95% CI [0.152, 0.289]) (see **Table 2**). The summary effect of standardized mean differences differed significantly across groups [$F_{(2, 504)} = 11.588$, $p < 0.001$] and was highest for combined *vs.* control comparisons ($g = 0.275$, $p < 0.001$, 95% *CI* [0.201, 0.359]), followed by combined *vs.* single physical training ($g = 0.21$, $p < 0.001$, 95% *CI* [0.128, 0.291]). On the other hand, the summary effect of cognitive outcomes for combined *vs.* single cognitive training was similar ($g = 0.083$, n.s., 95% CI [-0.001, 0.169]). The summary effect for physical outcomes ($k = 190$) was 0.285 ($p < 0.001$, 95% *CI* [0.192, 0.378]). Combined training produced a superior effect in all comparisons [$F_{(2, 187)} = 0.886$, *n.s.*], which was highest when compared to single cognitive training ($g = 0.33$, $p < 0.001$, 95% *CI* [0.171, 0.489]), followed by the comparison with control groups ($g = 0.30$, $p < 0.001$, 95% *CI* [0.198, 0.412]), and single physical training ($g = 0.218$, $p < 0.01$, 95% *CI* [0.073, 0.363]).

Regarding cognitive pre-follow-up outcomes ($k = 73$), we found a summary effect of 0.205 ($p < 0.01$, 95% *CI* [0.073, 0.338]). The differential effect of combined training differed across group comparison ($F_{(2, 70)} = 4.093$, $p < 0.05$), and was highest when compared to control groups ($g = 0.31$, $p < 0.01$, 95% *CI* [0.107, 0.513]), followed by single physical training ($g = 0.239$, $p < 0.05$, 95% *CI* [0.037, 0.442]). Combined training did not show superior effects at

TABLE 1 | Study designs and descriptive data of the primary studies included in the meta-analysis.

References	Country	*N*	Groups (n, M_{age})	No. of sessions	Duration (wks)	Follow-up (wks)	Cognitive intervention			Physical intervention				Combinatory mode	Setting	Control activities/ other components	Outcome measures
							Description	min/wk	Trained functions	Description	min/wk	Trained functions	Aerobic intensity				
Adcock et al. (2020)	Switzerland	31	EI-CI (15, 77) PC (16, 70.9)	48	16	-	Square stepping, 3 d/wk	95	EF, attention	Tai Chi-inspired movements and dancing 3 d/wk	105	Strength, balance, fitness	Low	Simultaneous	Individual	-	**Cognitive**: EF, PS, memory **Physical**: balance (gait), fitness
Anderson-Hanley et al. (2012)	USA	63	EI-CI (30, 76.1) EI (33, 81.7)	36	12	-	Exergames 3 d/wk, 2 months	135	Not clear	Stationary bicycle riding at 60% HRmax 3 d/wk for 3 months	135	Fitness	Moderate	Simultaneous	Individual	-	**Cognitive**: EF, global cognition, attention, language, memory
Andrieu et al. (2017)	France	722	EI-CI (356, 75) PC (366, 75.1)	745	144	-	Multicomponent exercises 1.5 d/wk during the first 2 months, 1 d/every 3rd mo. for the rest of the trial.	90	ES, PS, memory	Personalized home-based exercise program 5 d/wk	150	Fitness, balance, strength	Low	Separate	Mixed	-	**Cognitive:** global cognition, memory, PS language, attention, EF **Physical**: fitness
Bamidis et al. (2015)	Greece	90	EI-CI (69, n/a) PC (21, n/a)	37 CI: 14, EI:23	9	-	Computerized cognitive training (Posit Science), 3 d/wk	180	EF, memory	Exergames (FitForAll for Wii) at 55–85% HRmax, 2.3 d/wk	120	Fitness, balance, strength	Moderate	Not clear	Group	-	**Cognitive**: composite score of EF and memory
Barban et al. (2017)	Italy, Greece, Spain, Serbia	481	EI-CI (121, 74.5) EI (119,75.5) CI (118, 74.1) CC (123, 76)	24	12	12	Computerized cognitive training 2 d/wk	EI-CI:60 CI:120	EF, memory	Supervised structured exercise program with i-walker. 2 d/wk	EI-CI:60 EI:120	Balance, fitness	Low	Sequential	Mixed	CC: entering data into computer	**Cognitive**: memory
Desjardins-Crépeau et al. (2016)	Canada	76	EI-CI (22, 72.7) EI-CC (16, 70.9) EC-CI (20, 73.2) EC-CC(18, 72.5)	36	12	-	Computer tasks 1 d/wk	60	EF, attention	Supervised structured exercise program and treadmill walking 2 d/wk	120	Fitness, strength	Moderate	Sequential	Group	EC: Stretching, toning CC: Computer lessons	**Cognitive**: ES, memory, PS **Physical**: fitness, balance, strength
Eggenberger et al. (2015)	Switzerland	47	EI-CI (22, 78.5) EI (25, 80.8) DANCE not incl.	52	26	24	Computer tasks 2 d/wk	120	Memory	Structured exercise program and treadmill walking 2 d/wk	120	Fitness, strength, balance	Moderate	Simultaneous	Mixed	-	**Cognitive**: memory, attention, EF, PS
Fabre et al. (2002)	France	32	EI-CI (8, 64.9) CI (8, 67.5) EI (8, 65.4) AC (8, 65.7)	24	8	-	Multicomponent exercises 1 d/wk	90	Memory, attention, language	Supervised outdoor interval training at ventilatory threshold 2 d/wk	120	Fitness	Moderate	Separate	Group	AC: leisure activities	**Cognitive**: memory **Physical**: fitness
Gill et al. (2016)	Canada	44	EI-CI (23, 72.6) EI (21, 74.5)	78	26	-	Verbal exercises 3 d/wk	45	EF, language	Structured aerobic exercise at 70–85% HRmax and beginner-level square stepping 3 d/wk	120	Fitness	Moderate	Simultaneous	Mixed	-	**Cognitive**: EF, PS, memory, language
Gschwind et al. (2015)	Spain, Germany, Australia	153	EI-CI (78, 74.7) PC (75, 74.7)	42	16	-	Computerized exercises 2.5 d/wk	100	EF, attention	Individualized training protocol embedded in home-based exergames 2.5 d/wk	112	Strength, balance	None	Simultaneous	Individual	-	**Cognitive**: EF, PS, attention. **Physical**: balance, fitness, strength

(Continued)

TABLE 1 | Continued

References	Country	*N*	Groups (n, M_{age})	No. of sessions	Duration (wks)	Follow-up (wks)	Cognitive intervention			Physical intervention				Combinatory mode	Setting	Control activities/ other components	Outcome measures
							Description	min/wk	Trained functions	Description	min/wk	Trained functions	Aerobic intensity				
Hiyamizu et al. (2012)	Japan	36	EI-CI (17, 72.9) EI (19, 71.2)	24	12	-	Verbal exercises 2 d/wk	120	EF, attention, language	Supervised structured exercise program 2 d/wk	120	Strength, balance	None	Simultaneous	Group	-	**Cognitive**: EF, PS **Physical**: balance, strength
Htut et al. (2018)	Myanmar	42	EI-CI (21, 75.8) PC (21, 76)	24	8	-	Exergames 3 d/wk	90	PS, attention	Exergames 3 d/wk	90	Balance, fitness	Low	Simultaneous	Individual	-	**Cognitive**: global cognition **Physical**: balance, strength
Jardim et al. (2021)	Brazil	72	EI-CI (41, 67.4) PC (31, 67.9) EI + CI not incl.	24	12	-	Verbal exercises, psychomotor tasks 2 d/wk	150	EF, memory, attention, language	Supervised structured exercise program at 60–70% HRmax 2 d/wk	150	Fitness, balance, strength	Moderate	Simultaneous	Group	-	**Cognitive:** memory, attention **Physical:** fitness, balance, strength
Jehu et al. (2017)	Canada	41	EI-CI (14, 68.7) EI (15, 70.2) PC (12, 66.3)	36	12	12	Verbal exercises 3 d/wk	180	EF, language	Supervised structured exercise program 3 d/wk	180	Balance	None	Simultaneous	Individual	-	**Cognitive**: EF **Physical**: balance
Joubert and Chainay (2019)	France	48	EI-CI (16, 69.4) PC (16, 69.8) CI (16, 69.5)	16	8	4	Home-based computerized cognitive training (HAPPY neuron Professional) EI-CI: 1 d/wk CI: 2 d/wk	EI-CI:60 CI:120	EF	Supervised treadmill walking 1 d/wk	60	Fitness	Moderate	Separate	Individual	-	**Cognitive**: EF, language
Kitazawa et al. (2015)	Japan	60	EI-CI (30, 76.8) PC (30, 75.5)	8	8	-	Square stepping 1 d/wk	60	Memory	Supervised square stepping 1 d/wk	60	Fitness, balance	Low	Simultaneous	Group	-	**Cognitive**: global cognition, memory **Physical**: balance
Laatar et al. (2018)	Tunisia	24	EI-CI (12, 66.3) EI (12, 67, 45)	72	24	12	Verbal exercises, psychomotor tasks 3 d/wk	180	EF, memory, attention	Supervised structured exercise program 3 d/wk	180	Strength, balance	None	Simultaneous	Group	-	**Cognitive**: PS **Physical**: fitness, balance (gait), strength
Legault et al. (2011)	USA	67	EI-CI (18, 75.4) CI (16, 76.0) EI (16, 77.5) AC (17, 76.9)	56	16	-	Center-based computer tasks 1.5 d/wk	100	Memory	Center-based and home-based exercises including walking or stationary cycling 2 d/wk	150	Fitness	Moderate	Separate	Mixed	AC: Health education	**Cognitive**: EF, memory
Linde and Alfermann (2014)	Germany	55	EI-CI (16, 65.6) EI (15, 68.3) CI (11, 67.3) PC (13, 66.6)	32	16	12	Multicomponent exercises 1 d/wk	30	EF, PS, memory, attention	Supervised structured exercise program at 40% to 70% HRmax. 2 d/wk	120	Fitness, strength	Moderate	Sequential	Group	-	**Cognitive**: EF, memory, attention, PS **Physical**: fitness
Maillot et al. (2012)	France	30	EI-CI (15, 73.5) PC (15, 73.5)	24	12	-	Exergames 2 d/wk	120	Not clear	Wii exergames 2 d/wk	120	Fitness, balance	Not clear	Simultaneous	Not clear	-	**Cognitive**: EF, PS **Physical**: fitness, strength
Marmeleira et al. (2009)	Portugal	32	EI-CI (16, 68.4) PC (16, 68.2)	36	12	-	Psychomotor tasks 3 d/wk	180	EF, PS, attention	Psychomotor responses to cognitive demands (walking, catching balls, etc.) 3 d/wk	180	Fitness	Low	Simultaneous	Group	-	**Cognitive**: attention, EF, PS **Physical**: fitness, balance

(Continued)

TABLE 1 | Continued

References	Country	*N*	Groups (n, M_{age})	No. of sessions	Duration (wks)	Follow-up (wks)	Cognitive intervention			Physical intervention				Combinatory mode	Setting	Control activities/ other components	Outcome measures
							Description	min/wk	Trained functions	Description	min/wk	Trained functions	Aerobic intensity				
McDaniel et al. (2014)	USA	79	EI-CI (19, 6) EI-CC (23, 7) CI-EC (18, 6) CC-EC(19, 6)	96	24 (CI: 2 EI: 6)	-	Multicomponent exercises 3 d/wk	180	EF, memory, attention	Supervised treadmill walking or stationary cycling at 50% to 85% HRmax. 3 d/wk	180	Fitness	Moderate	Sequential	Group	EC: Flexibility CC: Health education	**Cognitive**: attention, memory **Physical**: VO_2 peak
Morita et al. (2018)	Japan	19	EI-CI (8, 75) PC (11, 71.9)	96	96	-	Verbal exercises, psychomotor tasks 1 d/wk	60	EF, memory, language	Supervised structured exercise program 1 d/wk	60	Fitness, strength	Low	Simultaneous	Group	-	**Cognitive**: global cognition **Physical**: strength, fitness, balance
Ng et al. (2018)	Singapore	197	EI-CI (49, 70.4) EI (48, 70.2) CI (50, 69.7) AC (50, 70.2)	30	24	24	Multicomponent exercises 120 min, 1 d/wk for 12 weeks plus 6 booster sessions	120	EF, PS, attention, memory, language	Structured exercise program center-based:2 d/wk for 12 weeks; 12 wk. home-based sessions; number not clear.	180	Strength, balance	None	Separate	Mixed	AC: Leisure activities	**Cognitive**: global cognition, memory, language, attention, EF
Ngandu et al. (2015)	Finland	1,190	EI-CI (591, 69.5) AC (599, 69.2)	538	96	-	10 group-based sessions on memory and reasoning strategies, and 2 x 6 months 72 (10–15 min, 3 d/wk) home-based, computerized training.	37	EF, PS, memory, attention	Center-based supervised, structured, and individualized exercise program 3–5 d/wk	not clear	Fitness, strength	Not clear	Separate	Mixed	AC: Health education	**Cognitive**: global cognition, EF, PS, memory
Nilsson et al. (2020)	Sweden	73	EI-CI (25, 70.3) CI (21, 70.9) EI (27, 70.3)	30	12	-	Computerized working memory training 2.5 d/wk	75	EF	Supervised interval training on stationary bikes at 65–75% HRmax. 2.5 d/wk	90	Fitness	Moderate	Sequential	Group	-	**Cognitive**: EF, PS, memory, language
Nishiguchi et al. (2015)	Japan	48	EI-CI (24, 7) PC (24, 73.5)	12	12	-	Verbal exercises, psychomotor 1 d/wk	60	EF, language	Group classes with music soundtrack 1 d/wk	90	Fitness, strength	Not clear	Simultaneous	Group	-	**Cognitive**: global cognition, memory, EF **Physical**: fitness, balance, strength
Nocera et al. (2020)	USA	37	EI-CI (13, 72.1) EI (12, 69.5) CI-EC (12, 7)	36	12	-	Computerized cognitive training (Mindfit) 3 d/wk	60	EF and "other processes"	Supervised stationary bicycle riding at 50 to 75% HRmax. 3 d/wk	135	Fitness	Moderate	Sequential	Group	EC: Stretching	**Cognitive**: EF, memory, language, PS **Physical:** fitness, balance (gait)
Norouzi et al. (2019)	Iran	40	EI-CI (20, 68.5) AC (20, 68.1) EC not incl.	12	4	12	Verbal and visual tasks 3 d/wk	210	EF, memory	Supervised strength training using an isokinetic exercise device. 3 d/wk	210	Strength	None	Simultaneous	Group	AC: group discussions	**Cognitive**: EF, memory **Physical**: strength

(Continued)

TABLE 1 | Continued

References	Country	N	Groups (n, M_{age})	No. of sessions	Duration (wks)	Follow-up (wks)	Cognitive intervention			Physical intervention				Combinatory mode	Setting	Control activities/ other components	Outcome measures
							Description	min/wk	Trained functions	Description	min/wk	Trained functions	Aerobic intensity				
Oswald et al. (2006)	Germany	196	EI-CI (24, 79.5) EI (29, 79.5) CI (46, 79.5) PC (97, 79.5)	30	48	48	Multicomponent exercises 1 d/wk	45	Memory, attention, PS	Supervised exercise program including gymnastics, dance, games, tennis skills, etc. 1 d/wk	45	Balance, fitness	Low	Sequential	Group	-	**Cognitive**: composite score from multiple test-domains **Physical**: composite score from multiple test-domains
Phirom et al. (2020)	Thailand	39	EI-CI (19, 70.2) PC (20, 69.4)	36	12	-	Exergames 3 d/wk	180	EF, memory, attention	Center-based exergames (Xbox) 3 d/wk	180	Fitness, balance	Low	Simultaneous	Group		**Cognitive**: global cognition **Physical**: balance, strength
Pieramico et al. (2012)	Italy	30	EI-CI (15, 67.5) PC (15, 67.5)	144	24	-	Home-based cognitive activities 5 d/wk, and group activities 120 min, twice a month	300	Not clear	Structured home-based walking and dancing 2 d/wk	120	Fitness	Low	Separate	Mixed	-	**Cognitive**: global cognition, EF, memory, language, PS
Rahe et al. (2015a)	Germany	45	EI-CI (25, 68.4) CI (20, 67.6)	14	7	-	Multicomponent exercises 2 d/wk	140	Memory, EF, attention	Group classes and home exercises (walking, taking stairs) 2 d/wk	40	Fitness, balance, strength	Low	Sequential	Group	-	**Cognitive**: global cognition, memory, EF, language, attention **Physical**: fitness, strength
Rahe et al. (2015b)	Germany	30	EI-CI (15, 67.1) CI (15, 66.3)	13	6.5	48	Multicomponent exercises 2 d/wk	190	Memory, EF, attention	Supervised structured exercise program 2 d/wk	40	Fitness, balance, strength	Low	Sequential	Group	-	**Cognitive**: global cognition, EF, language, attention
Raichlen et al. (2020)	USA	51	EI-CI (12, 67.7) EI (17, 68.1) CI (10, 66.4) AC (12, 69.3)	36	12	-	Computerized cognitive training 3 d/wk	90	EF, PS, memory,	Supervised stationary bicycle riding at 40–80% HRmax 3 d/wk	90	Fitness	Moderate	Simultaneous	Group	AC: watching videos	**Cognitive**: EF **Physical**: balance (gait)
Romera-Liebana et al. (2018)	Spain	352	EI-CI (176, 77.2) PC (176, 77.4)	24	12	18	Multicomponent memory and verbal training 2 d/wk	180 (6 wks)	Memory, language	Supervised structured exercise program 2 d/wk	120 (6 wks)	Fitness, balance, strength	Not clear	Separate	Group	Nutritional supplement	**Cognitive**: memory, language **Physical**: fitness, balance, strength
Salazar-González et al. (2015)	Mexico	286	EI-CI (143, 71) PC (143, 74)	36	12	-	Verbal exercises, psychomotor tasks 3 d/wk	60	EF	Supervised structured exercise program 3 d/wk	180	Fitness, balance, strength	Low	Simultaneous	Group	-	**Cognitive**: EF **Physical**: Balance (gait)
Schoene et al. (2013)	Australia	32	EI-CI (15, 77.5) PC (17, 78.4)	22	8	-	Home-based exergame (Stepmania) 1.5 d/wk	30	EF	Home-based exergames involving step exercises 1.5 d/wk	30	Fitness	Low	Simultaneous	Individual	-	**Cognitive**: PS, EF **Physical:** balance (+postural stability), strength
Schoene et al. (2015)	Australia	81	EI-CI (39, 82.7) PC (42, 81)	48	16	-	Home-based exergames	60	EF, PS, attention	Home-based exergames	60	Fitness	Low	Simultaneous	Individual	-	**Cognitive**: EF, PS

(Continued)

TABLE 1 | Continued

References	Country	*N*	Groups (n, M_{age})	No. of sessions	Duration (wks)	Follow-up (wks)	Cognitive intervention			Physical intervention				Combinatory mode	Setting	Control activities/ other components	Outcome measures
							Description	min/wk	Trained functions	Description	min/wk	Trained functions	Aerobic intensity				
							(Stepmania, Trail-Stepping, Stepper, Tetris), 3 d/wk			involving step exercises 3 d/wk							
Shah et al. (2014)	Australia	172	EI-CI (44, 67.2) EI (42, 67.4) CI (51, 66.6) PC (35, 69.1)	160	16	-	Computerized cognitive training (Posit Science) 5 d/wk	300	Not clear	Supervised structured exercise program 5 d/wk	250	Fitness, strength	Low	Sequential	Individual	-	**Cognitive**: memory, language, PS, attention, EF **Physical:** fitness, strength
Shatil (2013)	USA	122	EI-CI (29, 79) EI (31, 79) CI (33, 80) AC (29, 81)	96	16	-	Computerized cognitive training (CogniFit) 3 d/wk	120	EF, PS, attention, language, memory	Supervised structured exercise program (FitnessForever™) 3 d/wk	135	Fitness, strength	Low	Separate	Group	AC: book reading	**Cognitive**: Memory, attention, EF, PS
Takeuchi et al. (2020)	Japan	93	EI-CI (30, 68) CI (30, 68.8) EI (33, 69.3)	36	12	-	Computerized cognitive training (Brain Age, Nintendo) 3 d/wk	180	EF	Center-based supervised stationary bike riding at 40–50% HRmax 3 d/wk	90	Fitness	Low	Simultaneous	Not clear	-	**Cognitive**: Memory, attention, EF, PS, language
Teixeira et al. (2013)	Brazil	41	EI-CI (21, 68.2) PC (20, 67.9)	48	16	-	Square stepping 3 d/wk	120	Attention, memory, EF	Supervised, structured square stepping exercises 3 d/wk	120	Strength, balance	None	Simultaneous	Group	-	**Cognitive**: global cognition, EF, memory, attention, PS
Theill et al. (2013)	Switzerland	51	EI-CI (18, 72.4) CI (12, 73.3) PC (21, 70.9)	20	10	-	Computerized working-memory training 2 d/wk	60	EF	Supervised center-based-treadmill walking at 60–80% HRmax 2 d/wk	80	Fitness	Moderate	Simultaneous	Not clear	-	**Cognitive**: attention, memory, EF, PS **Physical**: balance (gait)
van Het Reve and de Bruin (2014)	Switzerland	145	EI-CI (69, 81.1) EI (76, 81.9)	84	12	-	Computerized cognitive training (CogniPlus) 3 d/wk	30	Attention	Progressive strength training and balance training. 2 d/wk	80	Balance, strength	None	Sequential	Not clear	-	**Cognitive**: EF, attention **Physical:** balance (gait), fitness
Wollesen et al. (2017)	Germany	83	EI-CI[b] (30, 69.8) PC[b] (18, 72.7) EI-CI[c] (15, 72.2) PC[c] (20, 72)	12	12	-	Psychomotor tasks 1 d/wk	60	EF, attention	Supervised walking exercises 1 d/wk	60	Fitness	Low	Simultaneous	Group	-	**Cognitive**: EF **Physical**: balance (gait), fitness
Wongcharoen et al. (2017)	Thailand	45	EI-CI (15, 71.9) EI (15, 73.5) CI (15, 72.4) CI dual-task not incl.	12	4	-	Cognitive tasks 3 d/wk	180	Attention, memory, language	Home-based stance and gait activities 3 d/wk	180	Balance	None	Simultaneous	Mixed	-	**Cognitive**: EF, language **Physical**: balance (gait)
Yokoyama et al. (2015)	Japan	25	EI-CI (12, 74.2) EI (13, 74.2)	48	12	-	Verbal exercises, psychomotor tasks 3 d/wk	180	EF	Supervised structured exercise program 3 d/wk	180	Fitness, balance	None	Simultaneous	Group	-	**Cognitive**: global cognition, PS **Physical:** strength, fitness, balance
You et al. (2009)	South Korea	13	EI-CI (8, 68.3) EI-CC (5, 68)	18	6	-	Verbal exercises 3 d/wk	90	EF, memory	Supervised fast walking 3 d/wk	90	Fitness	Moderate	Simultaneous	Not clear	CC: Music	**Cognitive**: memory **Physical:** balance (gait)
Yu et al. (2021)	China	347	EI-CI[d] (117, 64.7) EI-CC (114, 64) EI-CI[e] (116, 64)	24	12	-	Computerized cognitive training (Brainastic) 2 d/wk	60	EF, memory, attention	Aerobic circuit and resistance training 2 d/wk	120	Fitness, strength	Moderate	Sequential	Group	CC: DVDs	**Cognitive**: global cognition, memory

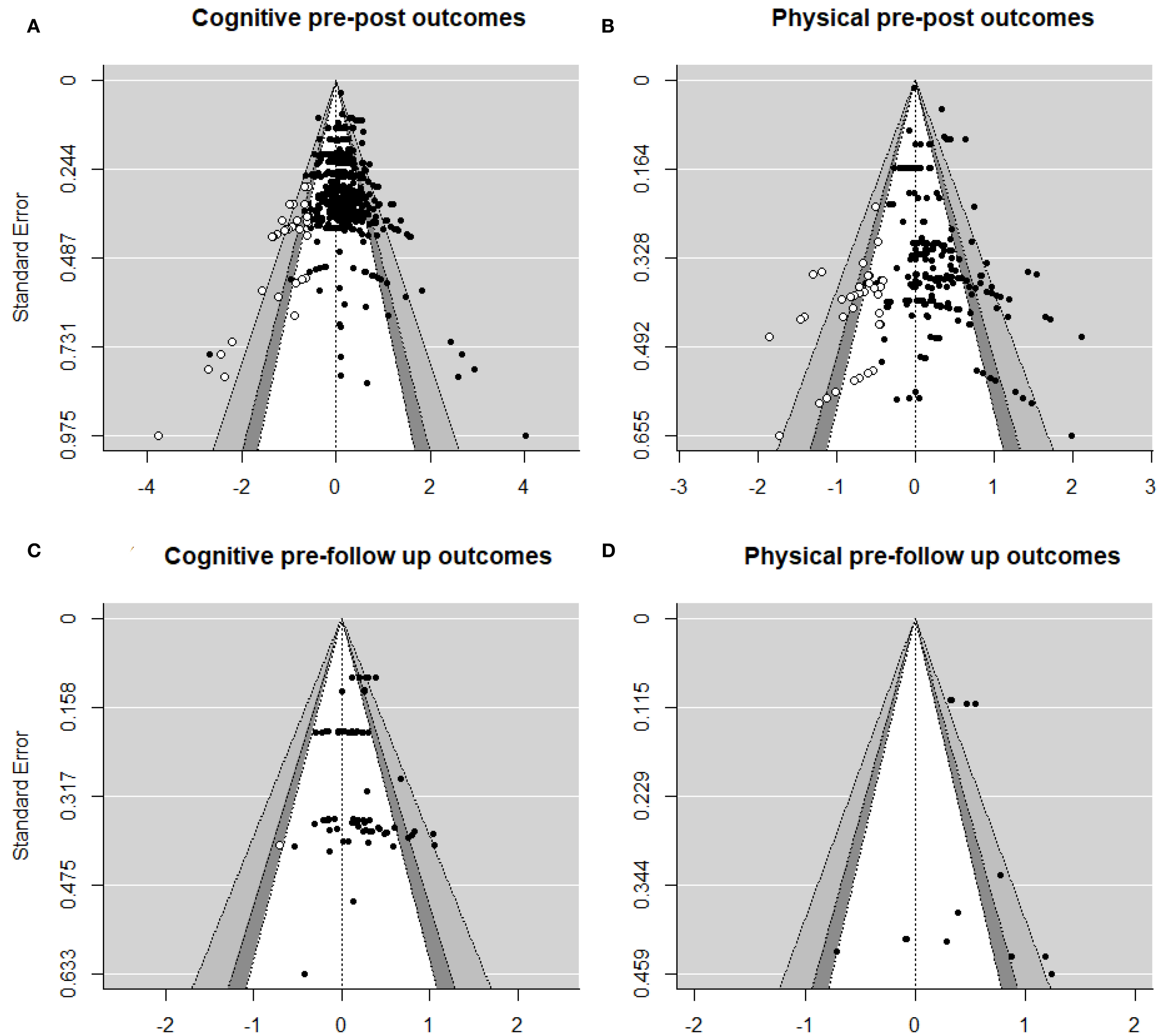

FIGURE 2 | Funnel plots with ES on the X-axis and standard error of the ES on the Y-axis for the estimated summary effects of **(A)** cognitive, **(B)** physical pre-post outcomes, **(C)** cognitive, and **(D)** physical pre-follow up outcomes.

follow-up when compared to single cognitive training $(g = 0.073, n.s., 95\%\ CI\ [-0.128, 0.275])$. Only 4 studies reported results of physical pre-follow-up assessments. Also, no ES was reported for a combined *vs.* single cognitive comparison. For combined *vs.* single physical training and control group comparisons, the summary effect was 0.417, with no significant group differences ($F_{(2,\ 11)} = 1.462$, *n.s.*). Nonetheless, due to the low number of effect sizes ($k = 13$), this result should be interpreted with caution. Combined training produced a significant superior effect when compared to control groups $(g = 0.584, p < 0.01, 95\%\ CI\ [0.199, 0.968])$, however, the comparison with single physical training did not reach statistical significance $(g = 0.243, p = n.s., 95\%\ CI\ [-0.259, 0.745])$. Given the low number of ES, we did not analyze the follow-up results by functions, as most categories x group combination contained less than three ES.

According to Hunter and Schmidt (1990), heterogeneity can be regarded as substantial if sampling variance (variance explained by the specific participants sampled in the experiment) is below 75%. This criterion was achieved for both of our main conditions (cognitive and physical pre-post ES), justifying our three-level meta-analytic approach. In both cases, the three-level model provided a significantly better fit compared to a two-level model with level 3 heterogeneity constrained to zero, as indicated by the likelihood ratio test (LRT) ($cognitive: \chi^2_1 = 7.554$, $p < 0.001$, $physical: \chi^2_1 = 47.909$, $p < 0.001$). Also, the Akaike (AIC) and Bayesian Information Criterion

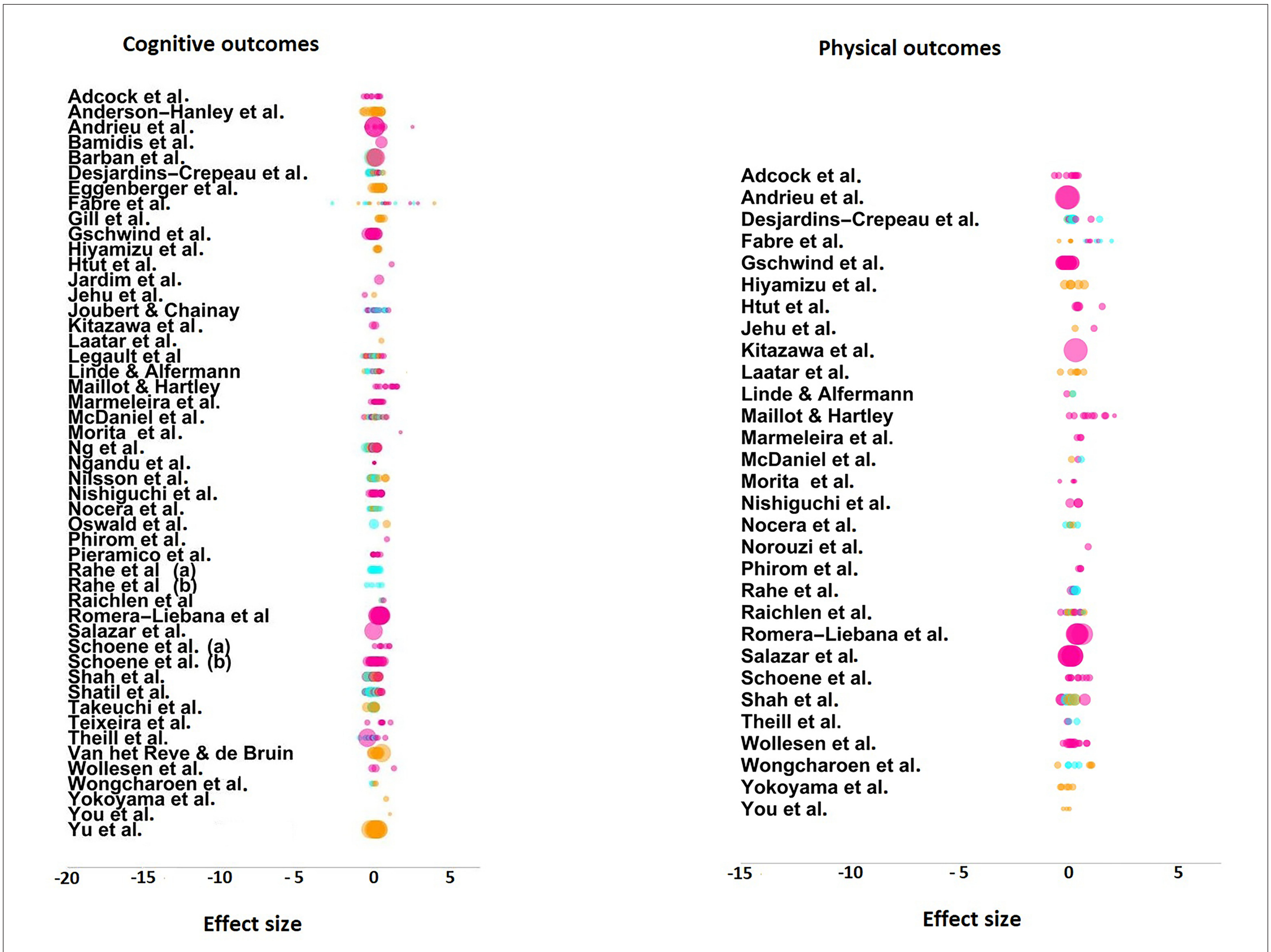

FIGURE 3 | Dot-plot figures for effect sizes for cognitive outcomes and physical outcomes by primary studies. Pink dots represent combined training *vs.* control, blue dots represent combined *vs.* single cognitive training, and orange dots, combined *vs.* single physical training. The size of the dot indicates the inverse of the ES variance scaled and represents the precision of the ES.

(BIC) were lower for the three-level models, indicating improved model fits. On the other hand, we found in both conditions (cognitive and physical pre-post ES) a relatively high variance attributable to the estimated sampling variance and the between-study variability, but very little (4.9% for cognitive pre-post outcomes), or none of the proportion (for physical pre-post outcomes) explained by the within-study level. The low level 2 variance suggests that the differences in effect sizes within each study were consistent across the comparison groups. On the other hand, approximately half of the studies included only one type of comparison and, for the other half, two or more types of comparisons (see **Table 1** with the descriptive data). Thus, the source of the level 3 variance could be attributable to a combination of the differential treatment effects (e.g., combined *vs.* control from one study, combined *vs.* single cognitive from another study, etc.), and different effect size magnitudes across studies (e.g., combined *vs.* control from several studies).

Moderator Analyses

Pre-post Training Effects by Cognitive Function

We analyzed the training effects on seven categories of cognitive functions (executive functions, attention, memory, language, processing speed, global functioning, and composite scores) using REML as the estimation method. These seven categories were crossed with the standardized mean difference of effect sizes of group comparisons (combined *vs.* single cognitive, combined *vs.* single physical, and combined *vs.* control). Their means, confidence intervals, statistical significance, as well as QE-values as a test of heterogeneity for all effect sizes, and the level 2 and level 3 variances are displayed in **Table 3**.

In executive functions, combined training achieved superior effects in comparison to control groups $(g = 0.201,\ p < 0.001)$, single physical $(g = 0.199,\ p < 0.01)$, and single cognitive training $(g = 0.144,\ p < 0.05)$. In memory and speed, combined training produced superior training effects compared to control groups ($g = 0.204$, $p < 0.001$ and $g = 0.308, p < 0.001$,

TABLE 2 | Summary effect of pre-post and pre-follow up comparisons of pooled cognitive and physical differences of effect sizes, respectively.

	Comparison	Level 2 variance (%)	Level 3 variance (%)	QE	# Studies	# ES	Mean difference in ES [95% CI]
Cognitive functions	Pre-post	0.005 (4.9)	0.041 (36.991)***	791.173***	49	507	0.22 [0.152, 0.289]***
	Pre-follow up	0.000 (5.326e-09)	0.026 (35.619)**	71.335	10	73	0.205 [0.073, 0.338]**
Physical functions	Pre-post	0.000 (7.649e-08)	0.045 (54.278)***	424.825***	30	190	0.285 [0.192, 0.378]***
	Pre-follow up	0.003 (7.842)	0.000 (1.021e-07)	21.622*	4	13	0.417 [0.297, 0.538]***

*#Studies, Number of studies; #ES, Number of effect sizes; ES, Hedges' g; CI, Confidence interval; Level 2 variance, Variance in effect sizes within studies; Level 3 variance, Variance in effect sizes between studies; %, Proportion of the total variance of effect sizes attributed to this level; QE, test for heterogeneity in all effect sizes in the data set. *p < 0.05; **p < 0.01; ***p < 0.001.*

for memory and speed, respectively), and to single physical training ($g = 0.137, p < 0.05$ and $g = 0.258$, $p <$ 001, for memory and speed, respectively), whereas no significant differences were found in these categories when compared to single cognitive training ($g = 0.007$, n.s., and $g = 0.046$, n.s., for memory and speed, respectively). In attention, language, and global cognition, combined training only produced superior effects when compared with control groups ($g = 0.197$, $p < 0.05$, $g = 0.305, p < 0.01$ and $g = 0.525$, $p < 0.01$, for attention, language, and global cognition, respectively). No other statistically significant differences were found.

Pre-post Training Effects by Physical Function

We analyzed the effect of the three training categories on the physical functions assessed in the original studies (balance, fitness, and strength), crossed with the type of training (combined, cognitive, and physical). Combined training showed significantly superior effects in comparison to control groups in fitness ($g = 0.242$, $p < 0.01$), balance ($g = 0.273$, $p < 0.001$), as well as in strength $(g = 0.372, \ p < 0.01)$. Furthermore, combined training showed an advantage over single physical training in balance ($g = 0.229$, $p < 0.05$), and over single cognitive training in fitness ($g = 0.338$, $p < 0.01$). No other group comparisons resulted statistically significant.

Design, Study Quality, and Sample Characteristics

We identified several study characteristics that could potentially modify the training outcomes (see **Supplementary Tables S5, S6** for detailed information).

Combinatory mode. Combined physical and cognitive training could be performed simultaneously (cognitive and physical training was performed at the same time), sequential (one after another) or separate (on different days). Our results indicated that the largest training effects in executive functions were produced by simultaneous training ($g = 0.208$, $p < 0.001$), followed by training on separate days ($g = 0.175$, $p < 0.05$). Sequential training did not produce a significant effect size in this case $g = 0.157$, $p > 0.05$). In attention, simultaneous $(g = 0.144, \ p < 0.05)$, as well as sequential training $(g = 0.286, \ p < 0.05)$, had an advantage over training on separate days $(g = -0.139, \ n.s.)$ $(F_{(2, \ 47)} = 4.483, p < 0.05)$. In speed, simultaneous training was related with an effect of 0.293 $(p < 0.01)$. Neither sequential training $(g = -0.007, n.s.)$, nor training on separate days $(g = 0.138, n.s.)$ were associated with significant training gains. In global cognition, simultaneous training resulted significantly superior $(g = 0.56, \ p < 0.05)$ to sequential $(g = 0.156, n.s.)$ and separate training $(g = 0.161, n.s.)$ $(F_{(2, \ 15)} = 41.064, p < 0.001.)$. As for the physical outcomes, only simultaneous training produced a significant effect size in outcomes that measured balance $(g = 0.259, \ p < 0.001)$ and strength $(g = 0.223, \ p < 0.05)$. No other significant differences were found.

Aerobic vs. Non-aerobic Training

Aerobic intensity was classified either based on objective measures provided by the authors (HRmax, velocity, etc.), or based on the description of the physical activities. Low to non-aerobic exercise, such as slow walking, strength, or balance training were classified as non-aerobic. Moderate to high aerobic intensity, such as walking at a fast pace or running were classified as aerobic. Gains in executive functions were larger for aerobic $(g = 0.20, \ p < 0.001)$ than for non-aerobic exercise $(g = 0.138, \ p < 0.01)$, even though the difference did not reach statistical significance $(F_{(2, \ 147)} = 0.732, n.s.)$. Aerobic exercise $(g = 0.279, \ p < 0.01)$ was related to more improvement in attention than non-aerobic exercise $(g = 0.032, n.s.)$ $(F_{(1, \ 48)} = 5.084, \ p < 0.05)$, whereas non-aerobic exercise produced larger effects in speed ($g = 0.202$, $p < 0.05$), and global cognition ($g = 0.508$, $p < 0.01$). In physical categories, as could be expected, aerobic training was related to higher gains in fitness $(g = 0.257, \ p < 0.01)$ than non-aerobic training $(g = 0.059, n.s.)$, and non-aerobic exercise produced larger gains in balance ($g = 0.272, p < 0.001$ and $g = 0.182$, n.s., for non-aerobic and aerobic, respectively). No other significant results were found in this category.

Type of Cognitive Training

Cognitive training was categorized as computer training (commercial videogames or tailor-made computer tasks), interactive training (dual-task paradigms in which the cognitive training part is intrinsically associated with a motor response, as in exergames, square stepping, etc.), and multicomponent training (which could be either a mixture of different training modalities, such as paper-pencil tasks, computer games, verbal exercises, etc., or only verbal exercises, such as counting backward, naming words according to a given classification, etc.). Interactive training produced a significantly higher effect on speed ($g = 0.494$, $p < 0.001$) than multicomponent ($g = 0.312, p < 0.05$) and computer training ($g = 0.042$, n.s.)

TABLE 3 | Results of moderator analyses for pre-post comparisons between combined training vs. control, cognitive or physical single for cognitive and physical outcomes.

Outcomes	Level 2 variance (%)	Level 3 variance (%)	Omnibus test[a]	QE	Comparison groups	# Studies	# ES	Mean difference in ES [95% CI]
Cognitive functions								
Executive functions	0.00 (7.811e-08)	0.024 (22.971)***	$F_{(2,161)} = 0.42$, $p = 0.657$	189.618	Combined vs. control	21	80	0.2 [0.103, 0.297]***
					Combined vs. cognitive	13	44	0.144 [0.021, 0.267]*
					Combined vs. physical	14	40	0.199 [0.081, 0.316]***
Memory	0.000 (4.286e-08)	0.039 (36.098)***	$F_{(2,138)} = 5.051$, $p = 0.008$	251.221***	Combined vs. control	19	50	0.204 [0.088, 0.321]**
					Combined vs. cognitive	15	43	0.007 [-0.119, 0.134]
					Combined vs. physical	17	48	0.117 [-0.017, 0.256]*
Attention	0.019 (17.262)	0.02 (18.141)	$F_{(2,47)} = 5.176$, $p = 0.009$	71.632*	Combined vs. control	10	28	0.197 [0.038, 0.358]*
					Combined vs. cognitive	8	11	−0.166 [-0.383, 0.051]
					Combined vs. physical	7	11	0.19 [-0.015, 0.396]
Language	0.00 (7.64e-09)	0.036 (45.287)***	$F_{(2,31)} = 3.387$, $p = 0.047$	30.875*	Combined vs. control	6	11	0.305 [0.123, 0.487]**
					Combined vs. cognitive	9	11	−0.008 [-0.201, 0.186]
					Combined vs. physical	9	12	0.08 [-0.102, 0.264]
Speed	0.00 (1.312e-08)	0.104 (54.037)***	$F_{(2,88)} = 3.481$, $p = 0.035$	148.492**	Combined vs. control	15	47	0.308 [0.129, 0.486]***
					Combined vs. cognitive	9	19	0.046 [-0.163, 0.256]
					Combined vs. physical	14	25	0.258 [0.069, 0.447]**
Global cognition	0.000 (1.211e-08)	0.153 (86.725)*	$F_{(2,15)} = 1.655$, $p = 0.224$	44.504***	Combined vs. control	8	10	0.525 [0.172, 0.877]**
					Combined vs. cognitive[a]	1	1	NA
					Combined vs. physical	2	7	−0.048 [-0.621, 0.524]
Composite scores	0.052 (39.027)	0.019 (14.62)	$F_{(2,6)} = 2.884$, $p = 0.133$	16.743*	Combined vs. control	5	4	0.392 [-0.017, 0.8]
					Combined vs. cognitive[a]	3	3	NA
					Combined vs. physical[a]	2	2	NA
Physical functions								
Fitness	0.00 (2.848e-08)	0.059 (61.28)***	$F_{(2,62)} = 1.917$, $p = 0.156$	176.29***	Combined vs. control	16	33	0.242 [0.075, 0.409]**
					Combined vs. cognitive	8	18	0.338 [0.105, 0.571]**
					Combined vs. physical	9	15	0.064 [-0.185, 0.313]
Balance	0.00 (2.757e-08)	0.026 (30.205)***	$F_{(2,92)} = 0.192$, $p = 0.826$	130.952**	Combined vs. control	17	58	0.273 [0.149, 0.396]***
					Combined vs. cognitive	4	12	0.196 [-0.052, 0.444]
					Combined vs. physical	9	25	0.229 [0.045, 0.413]*
Strength	0.037 (18.584)	0.092 (46.711)	$F_{(1,27)} = 0.266$, $p < 0.768$	71.739***	Combined vs. control	12	20	0.372 [0.103, 0.642]**
					Combined vs. cognitive	3	5	0.463 [-0.081, 1.007]
					Combined vs. physical	5	7	0.227 [-0.177, 0.632]

*[a]ES differences were only calculated for analyses with more than 3 ES. #Studies, Number of studies; #ES, Number of effect sizes; mean ES, mean Hedges' g; CI, Confidence interval; Level 2 variance, Variance in effect sizes within studies; Level 3 variance, Variance in effect sizes between studies; %, Proportion of the total variance of effect sizes attributed to this level; QE, test for heterogeneity in all effect sizes in the data set. Omnibus-test of all coefficients in the model (excluding the intercept). *p < 0.05; **p < 0.01; ***p < 0.001.*

($F_{(2,88)} = 4.463, p < 0.05$). Regarding executive functions, interactive training produced an effect of $g = 0.322$ ($p < 0.001$), followed by computer training ($g = 0.131$, $p < 0.05$), and multicomponent training ($g = 0.137$, *n.s.*). Also, in global cognition, interactive training showed the highest effect ($g = 0.573, p < 0.001$). The ES from the interactive training type stemmed in 90% of the cases from combined *vs.* control comparisons, because the cognitive activity is intrinsically associated with a motor response, so that it is impossible to perform the cognitive part separately. To confirm that the differences in training gains as a function of cognitive training type were not influenced by the underlying group comparisons, we repeated the analysis in executive functions and speed only for those cases that had been computed from combined *vs.* control comparisons. In executive functions, only interactive training achieved a significant ES ($g = 0.318, p < 0.001$), whereas the training gains associated with computer training ($g = 0.114$, *n.s.*), and multicomponent training ($g = 0.136$, *n.s.*) were not significant. The same occurred with speed, with interactive training achieving a medium ES ($g = 0.475, p < 0.001$), in contrast with non-significant gains in the case of computer ($g = 0.055$, *n.s.*), and multicomponent training ($g = 0.34$, *n.s.*). On the other hand, multicomponent training was related with the highest effects in memory ($g = 0.196$, $p < 0.05$) and language ($g = 0.228$, $p < 0.05$), without reaching the other modalities statistical significance. In physical outcomes, interactive and multicomponent training were related with significant effects on balance ($g = 0.301$, $p < 0.001$ and $g = 0.269$, $p < 0.01$, for interactive and multicomponent training, respectively). Interactive and multicomponent training were also related with significant improvements in fitness ($g = 0.385$, $p < 0.01$ *and* $g = 0.288$, $p < 0.01$, *for interactive and multicomponent*, *respectively*). Furthermore, interactive training was related with a significant effect in strength ($g = 0.411$, $p < 0.05$).

Setting

The training could either be performed in groups, individually, or in a mixed setting (some sessions group based, and others conducted individually). Group setting produced significant effects in all cognitive categories as opposed to individual or mixed setting. In executive functions, only the ES of group setting ($g = 0.162$, $p < 0.001$) and individual training ($g = 0.151$, $p < 0.05$) resulted significant. Group training was related with an effect of $g = 0.182$ ($p < 0.01$) for memory, $g = 0.189$ ($p < 0.05$) for attention, and $g = 0.482$ ($p < 0.05$) for global cognition. In language and speed, mixed training produced superior effects ($g = 0.333$, $p < 0.05$, *and* $g = 0.348$, $p < 0.05$, for language and speed, respectively), than group training ($g = 0.207$, $p < 0.05$ *and* $g = 0.2411$, $p < 0.05$, for language and speed, respectively), and in both cases significantly superior to individual training ($g = 0.086$ *and* $g = 0.08$, *n.s.*). Group training could not be compared to the other settings in composite scores due to insufficient ES in these categories. Regarding the physical outcomes, group setting was consistently related with significant effect sizes in all physical categories ($g = 0.328$, $p < 0.001$; $g = 0.255$, $p < 001$; $g = 0.291$, $p < 0.05$, for fitness, balance, and strength, respectively), even though individual training also showed a significant effect on balance outcomes ($g = 0.242$, $p < 0.05$).

Continuous Moderators

We analyzed the influence of several continuous moderators crossed with the different cognitive and physical outcome measures. We found a significant negative relationship between the number of participants and attention, suggesting that studies with smaller samples produced larger ES (β = −0.003, $p < 0.001$, CI 95% [-0.004,−0,001]). Also, studies conducted earlier achieved higher ES in fitness($\beta = -0.035$, $p < 0.05$, CI 95% $[-0.068, -0.002]$), and studies with lower quality ($\beta = -0.039$, $p < 0.05$, CI 95% $[-0.07, -0.008]$), and higher variability in the age of participants ($\beta = -0.11$, $p < 0.05$, CI 95% $[-0.218, -0.002]$) were related to higher gains in balance. Other moderators (year of publication, quality, mean age, number and minutes of sessions, number of weeks) were not significant.

DISCUSSION

This systematic review and three-level meta-analysis investigated the effectiveness of combined physical and cognitive training on the cognitive and physical functions of healthy older adults. It included a total of 783 effect sizes from 50 intervention studies that investigated the differential effect of combining physical and cognitive training vs. its components alone or control groups. The included studies varied in their experimental design, and cognitive and physical activities were performed simultaneously, sequentially, or on different days, in groups or individually. Also, the cognitive training was delivered in different ways, such as via computer games, multicomponent activities, or interactively such as in exergames.

Overall Effect Sizes

In line with previous meta-analyses (Zhu et al., 2016; Gheysen et al., 2018; Guo et al., 2020), our results revealed a small advantage of combined training on cognitive outcomes, which was maintained over time as shown by the follow-up effect. When analyzing the differential training effect by subcategories (executive functions, memory, attention, speed, language, and global cognition), combined training produced overall larger effects than control groups. In memory and processing speed, combined training also showed an advantage over single physical training. Combined training also had a small but significant advantage over single cognitive training in executive functions, whereas in the remaining cognitive functions, the effect of single cognitive training was not enlarged by the addition of physical exercise. This suggests that physical activation might act as an aggregate for the improvement of executive functions, independently of other cognitive processes. Executive functions, and their measurement, are closely related to certain aspects of attention, such as selective and divided attention. Nonetheless, we found no significant difference between combined and single cognitive training in attention, which might be related to a minor number of cases in this category.

Training Transfer Between Cognitive and Physical Domains

In physical outcomes, combined training showed in all categories (fitness, balance, strength) an advantage over control groups. Furthermore, fitness was the only physical outcome category, in which combined training had a significant advantage over single cognitive training, indicating that combined groups, indeed, had improved their cardiovascular fitness more than single cognitive training groups. Combined training was also related to greater training gains in balance than single physical training. Given that both, combined and single physical training, performed the same type and dosage of physical exercise, and only differed in that one group additionally received cognitive training, we can speak of a transfer of cognitive training to physical balance outcomes. The transfer distance (considering near and far transfer as a continuum), depends on the degree of the interrelation of both domains. A growing body of research provides evidence of an interrelationship between cognitive processing and balance and gait in older adults (Hausdorff et al., 2005; Montero-Odasso et al., 2012; for a review, see Li et al., 2018). Especially higher cognitive functions, such as executive functions and attentional control, have been investigated in relation to postural instability, showing that, as executive functions decline with age, walking and balance become less automated and more cognitively taxing (Woollacott and Shumway-Cook, 2002). This relationship becomes especially visible in dual-task paradigms (i.e., the simultaneous performance of a cognitive task and a motor task) when older adults often tend to protect their motor functioning at the expense of the cognitive task when the situation involves a threat to balance (Schaefer and Schumacher, 2011). Consistent with the existing literature, our results confirmed that the largest training gains in executive functions were obtained when the cognitive training was delivered interactively.

Cognitive Training Type, Combinatory Mode, and Aerobic Intensity

We considered as interactive training, dual-task paradigms in which the cognitive training part is intrinsically associated with a motor response, as in exergames or square stepping. In executive functions, interactive training more than doubled the effect achieved by computerized cognitive or multicomponent/verbal training (cognitive interventions that included verbal exercises or a mixture of different cognitive training modalities). Also, in speed measures, interactive training achieved the highest ES, which was only comparable to that obtained by multicomponent training, whereas computer training did not produce any effect on speed. In some studies, the multicomponent/verbal training was very close to interactive training (e.g., You et al., 2009; Hiyamizu et al., 2012; Jehu et al., 2017) when cognitive tasks were performed jointly with motor tasks. This suggests that the positive effect on processing speed by cognitive-physical dual tasks is boosted by situations in which cognitive challenges are intrinsically associated with functional motor responses, as it occurs in interactive training. This interpretation is also supported by our findings that simultaneous training was the only combinatory mode that was significantly related to higher gains in processing speed. Intuitively, one could postulate that processing speed would be related to cardiorespiratory fitness, in terms of more sufficient energy delivery to cerebral substrates that sustain fluid information processing. However, aerobic, and non-aerobic exercise were associated with similar training gains in processing speed. Also, in executive functions, the difference of training gains as a function of aerobic intensity was not remarkable, even though aerobic exercise was associated with slightly higher ES. Paradoxically, given the close relationship between these functions, in attention, aerobic exercise was associated with significantly higher training gains than non-aerobic exercise. Only a few studies reported and controlled the aerobic intensity with objective methods and in most cases, it was subjectively estimated. Thus, our results on the influence of the aerobic exercise intensity should be interpreted bearing in mind these limitations.

On the other hand, the mode of combining cognitive and physical activities had no significant influence on executive functions. This is an intriguing finding, as interactive training is always performed simultaneously, which, as mentioned earlier, achieved a significantly higher ES in executive functions than computer and multicomponent/verbal training. In the case of interactive training, almost 90% of the computed ES stemmed from combined *vs.* control comparisons, which produced the largest between-group differences. This could undermine to a certain degree the differences found regarding the other cognitive training types, which in many cases stemmed from combined *vs.* single cognitive comparisons. It is not possible to equate interactive cognitive interventions with single cognitive interventions as the first ones are intrinsically associated with motor responses. However, an additional analysis with only combined *vs.* control comparisons for all three cognitive training types (interactive, computer, and multicomponent) corroborated the result that interactive training was related to significantly higher effect sizes in executive functions and speed than the other two cognitive training types.

Multicomponent/verbal training produced the highest ES in language, which might be explained by the fact that in several studies in this category, the cognitive training included verbal fluency tasks (e.g., Gill et al., 2016; Wongcharoen et al., 2017; Ng et al., 2018; Romera-Liebana et al., 2018). In memory, even though interactive and multicomponent training produced similar ES, only the latter resulted statistically significant, possibly due to a higher heterogeneity in ES in the interactive training groups. Furthermore, advantageous training gains in attention were related to aerobic exercise, as well as to sequential and simultaneous training. Within the four studies with a sequential approach, 9 out of the 14 ES stemmed from one study (McDaniel et al., 2014) and originated from a tailor-made task. Thus, this finding would require replication with standardized or more common tasks. Likewise, the results in global cognition and composite scores should be interpreted with caution due to a low number of ES. In global cognition, interactive training resulted most beneficial. However, computer and multicomponent/verbal training only reported 4 and 5 ES, respectively, leading to an extremely high between-study variance (87%). On the other hand, in composite scores, multicomponent training could not be compared to the other training types, as computer training only reported two and interactive training no ES.

Regarding the physical outcomes, simultaneous training was associated with higher gains in balance and strength, reflecting the number of studies in this category that were originally designed to investigate the influence of dual-tasking on gait and balance. In line with this finding, higher gains in balance were also related to non-aerobic exercise, whereas aerobic exercise was related to gains in fitness. Interactive and multicomponent/verbal training was associated with higher effect sizes in fitness and balance, and interactive training also with higher gains in strength, whereas there was no differential effect found in computer training. This is surprising, as in more than 75% of the physical ES from the studies with computerized training, the comparison group (control and single cognitive training) had not received any physical training, as opposed to the combined training group. A tentative interpretation for this result would be that those studies that included computer training, imposed an overall lower level of physical demands on their participants so that between-group differences diminished.

The Benefits of Group Setting

Finally, in all cognitive outcome categories, group setting, and in some categories also mixed setting, was associated with more training gains than when performing the training individually. This finding underscores the importance of social interaction in interventions with older adults. Physical improvements were also larger when participants trained in groups, indicating that social interaction contributes as a significant motivational factor for optimum attainment.

Continuous Moderators

The analysis of continuous moderators revealed a significant negative relationship between the number of participants and ES achieved in outcomes that measured attention, with studies with lower sample sizes reporting higher ES.

None of the other moderators (quality, year of publication, mean age, number of sessions, session duration, intervention length) showed a significant influence on the cognitive results, indicating that study design and sample characteristics were overall homogenous across studies. With regards to physical outcomes, our results indicated that older studies reported higher ES in fitness and that higher variability in the mean age and lower study quality were associated with higher ES in balance outcomes.

Publication Bias

As mentioned above, the training effects were not influenced by study quality. However, this finding needs to be interpreted with caution, as it could be influenced by publication bias (only studies with a robust study design were accepted for publication). Our results revealed that there was a risk of publication bias for training effects on cognitive, as well as on physical functions, and our estimated effect for these groups may differ from the true training effect. In particular, the large number of small-sample studies included in our analysis may have produced an overestimation of the summary effect. Nonetheless, it has been suggested that large estimates of between-study heterogeneity can cause regression asymmetry (Ioannidis and Trikalinos, 2007; Ioannidis, 2008). Indeed, our results indicated moderate to high between-study variability for cognitive and physical functions, which was larger for the latter one. The between-study heterogeneity in our analysis included on the one hand the differences in sample sizes, and on the other hand the variability between the types of comparison groups across studies. Therefore, the symmetry of the funnel plot might not constitute the most idoneous method to analyze the risk of bias. However, there is no current consensus on techniques to assess biases in three-level meta-analyses, and these results must therefore be interpreted with caution.

As far as we know, this is the first meta-analysis that controlled for equivalence of the training components in the different comparison groups. Thus, only those studies were considered for analysis, in which the physical training part of the combined group was identical to the physical exercise performed by the comparison group. Furthermore, this is the first time, that exercise intensity, as well as the type of cognitive training, are included as moderators, leading to more specific knowledge on the effects of combining both activities. Another strength of the present study is the use of a three-level meta-analytic approach to investigate the effectiveness of training in several cognitive functions and physical variables. This approach seems an effective alternative to classic meta-analysis when there is interdependence between effect sizes. Traditional univariate meta-analytic approaches assume that there is no dependence between effect sizes, and one common solution is to average the dependent effect sizes within studies into a single effect size by calculating an unweighted or—-less biased—-weighted average. When averaging or eliminating effect sizes in primary studies, there may not only be the problem of a lower statistical power due to information loss but informative differences between effect sizes are also lost and can no longer be identified in the analyses.

In sum, the results of this three-level meta-analysis indicate that even in advanced age, cognitive functioning can be improved by training, and that combined training produces a small advantage over single cognitive training on executive functions. Overall, we found evidence that a simultaneous combination of cognitive and physical activity is more effective in improving executive functions, attention, and processing speed, and that the achievement is highest when the training is performed in a social context.

Recommendations for Future Research

Even though the present study may have contributed with more precise information on the combinatory effect of physical exercise and cognitive training on cognitive functions in healthy older adults, several issues remain unexplained and should be addressed in future research. Most importantly, to truly differentiate between mere learning effects and synergistic training benefits, it is necessary to disentangle the transfer effects and separate between near and fare transfer. Furthermore, dual-task investigations have shown that concurrent physical and cognitive activity might produce conflicts in attentional resource allocation. Therefore, future studies should control for this potential influence in their research designs, because depending on the complexity of the physical exercise, the exercise could either boost or weaken the effect of cognitive training. Lastly, an emerging field investigates the effects of immersive virtual reality (IVR) on cognition (Burin and Kawashima, 2021), where physical activity is experienced by virtual simulation. The inclusion of this type of intervention could provide interesting information in future meta-analytic research.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: https://osf.io/582ur/?view_only=9e6a7dca659d48318faf1544cc7966e4.

AUTHOR CONTRIBUTIONS

JMR, SB, and JAR conceptualized the design. JAR and MM conducted the searches with the approval of the other two authors. JMR and JAR conducted the statistical analyses. SB and MM conducted the quality assessment of the reviewed articles. SB and JAR wrote the article. All authors read and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2022.838968/full#supplementary-material

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*References marked with an asterisk indicate studies included in this meta-analysis.

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The Neural Mechanism of Long-Term Motor Training Affecting Athletes' Decision-Making Function: An Activation Likelihood Estimation Meta-Analysis

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Decision-making is an advanced cognitive function that promotes information processes in complex motor situations. In recent years, many neuroimaging studies have assessed the effects of long-term motor training on athletes' brain activity while performing decision-making tasks, but the findings have been inconsistent and a large amount of data has not been quantitatively summarized until now. Therefore, this study aimed to identify the neural mechanism of long-term motor training affecting the decision-making function of athletes by using activation likelihood estimation (ALE) meta-analysis. Altogether, 10 studies were included and comprised a total of 350 people (168 motor experts and 182 novices, 411 activation foci). The ALE meta-analysis showed that more brain regions were activated for novices including the bilateral occipital lobe, left posterior cerebellar lobe, and left middle temporal gyrus (MTG) in decision-making tasks compared to motor experts. Our results possibly suggested the association between long-term motor training and neural efficiency in athletes, which provided a reference for further understanding the neural mechanisms of motor decision-making.

Keywords: decision-making, motor training, neuroimaging, brainmap, activation likelihood estimation (ALE), fMRI

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INTRODUCTION

Decision-making refers to the advanced cognitive function to process information in complex situations (Johnson, 2006). The motor has the characteristics of behavior initiation, memory, and decision-making that make it easy to observe or measure the results of decisions, thus motor psychologists consider that the most suitable for decision-making research is the field of sports (Raab et al., 2019). Numerous studies have shown that long-term motor training can substantially change the neurological activation of the cerebral cortex (Kelly and Garavan, 2005; Leff et al., 2011; Morgan et al., 2015; Fernandes et al., 2017). Presently, motor-induced decreases in activity might occur in brain areas related to visual processing, such as the occipital pole (Duru and Balcioglu, 2018) and occipital fusiform gyrus (Herold et al., 2020). Motor psychologists used the "neural efficiency" hypothesis to explain the result (Babiloni et al., 2010; Li and Smith, 2021). Neural efficiency refers to the phenomenon in which task execution becomes an automatic and neural activity in specific brain regions decreases as skill levels increase (Neubauer and Fink, 2009; Karim et al., 2017). Meanwhile, long-term motor training promoted the formation of internal models in the brain that enabled athletes to perform tasks in a relatively stable and efficient manner

(Imamizu et al., 2000). For example, a study on archers when performing aiming tasks found that experts invoked smaller and more focused neural networks, whereas novices activated a wide range of brain regions including superior frontal gyrus, inferior frontal gyrus, prefrontal lobe, primary motor cortex, superior parietal lobe and primary somatosensory cortex (Kim et al., 2014). In contrast, some authors have found that the ventromedial prefrontal cortex (Hiser and Koenigs, 2018), orbitofrontal cortex (Rudebeck and Rich, 2018), infralimbic cortex (Roughley and Killcross, 2021), and amygdala (Chang et al., 2015) were activated in experts during decision-making. To summarize, changes in cortical activation caused by extensive motor training might be to satisfy better decision-making.

An "expert-novice" paradigm has been developed in the field of motor cognition (Del Villar et al., 2007). An important approach to study the effect of motor training on cortical activation during executive decision-making was to recruit professionals with intensive motor experience (motor experts) as an experimental group and compare their brain activation with that of a control group (novices).

Currently, image fixation and eye-movement recording methods are mostly used to compare the decision-making function of experts and novices in different motor scenarios, yet these methods are likely to make the obtained data content inaccurate due to the subjectivity of the subjects (Brunyé and Gardony, 2017). The rapid development of neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) has informed further understanding of the neural mechanisms underlying the differences in decision-making behavior between experts and novices (Kable and Levy, 2015; Bertollo et al., 2020). However, these studies have reported inconsistent results, probably due to small samples or inconsistent analysis methods.

Several studies have found that in decision-making tasks, experts showed decreased activation in specific brain regions compared to novices (Del Percio et al., 2008; Babiloni et al., 2010; Blain et al., 2019). An fMRI study comparing the intensity of brain activation during the ball response task in table tennis players and non-athletes found that the bilateral middle frontal gyrus, right middle orbitofrontal area, left inferior temporal gyrus, left middle temporal gyrus, right angular gyrus, and bilateral lingual gyrus was significantly less activated in the players (Guo Z. et al., 2017) and similar results were found by another study (Kellar et al., 2018). These authors suggested that task-related brain networks were organized more centrally and efficiently as athletes improved their skills, so a possible reflected more efficient utilization of specific neural circuits or automation of task execution. A study investigated the brain activation of objects tracking decisions in basketball players and novices. The results showed that less cortical activation of the bilateral middle frontal gyrus, right middle orbitofrontal area, right paracentral lobe, right precuneus, left supramarginal gyrus, right angular gyrus, left inferior temporal gyrus, left middle temporal gyrus and bilateral lingual gyrus was observed in basketball players than in novices (Qiu et al., 2019). This might indicate that long-term motor training promoted higher decision-making efficiency and athletes did not need to use more information systems to make decisions from complex situations, which led to less activation of neural network areas associated with decision-making (Wang et al., 2017; Ludyga et al., 2020; Blazhenets et al., 2021).

However, two fMRI studies (Abernethy and Russell, 1987; Wong and Gauthier, 2010) showed that expert players were able to pick up more relevant information than novices in a selective decision-making task, electrophysiological data indicated more prefrontal positive activities in experts (Javier et al., 2014). Several recent studies have found that experts compared with novices could quickly perceive the actions of opponents and successfully respond, and the frontal areas were more activated, which might be related to the expert's better ability in action planning and action understanding (Callan and Naito, 2014; Okazaki et al., 2015; Vernon et al., 2018). A randomized controlled trial recruited 15 basketball expert athletes and 15 novices to participate in an action decision-making task to analyze the correlation between gaze behavior and decision-making. The results showed that expert athletes had stable gaze fixation, accurate rate, and activation in the inferior parietal lobe and inferior frontal gyrus compared to novices (Wu et al., 2013). This suggested that experts might need more activation in the brain's attention and sensorimotor networks to achieve better decision-making performance.

Taken together, the above evidence has suggested that long-term motor training could alter brain activation in decision-related areas, but the findings were inconsistent. On the other hand, in existing many imaging studies, there was a small sample size of subjects, and the selection of motor items, duration, and intensity of each motor also vary, which might lead to low statistical power and effect sizes and even inconsistent findings (Yarkoni, 2009). Therefore, to overcome the limitations of single studies and further elucidate the neural mechanisms underlying the effects of motor training on decision-making functions, an activation likelihood estimation (ALE) algorithm based on large amounts of data need to be introduced into the field of motor cognition (Yarkoni et al., 2011). The quantitative approach for ALE has been increasingly improved, obtaining rich information within the whole brain. Therefore, the current study applied the ALE method to compare brain activation differences between experts and novices during the execution of decision-related tasks. Our results provide a reference for further understanding the neural mechanisms of motor decision-making and promote the development of motor cognitive neuroscience.

According to the view of motor psychologists, athletes acquired motor skills through training rapid stimulus discrimination, decision-making, and specialized attention, but novices did not have. So they concluded that motor experts were better able to perform specific tasks with fewer neural resources, suggesting that long-term motor training could improve the neural efficiency of experts, reflecting the automation process of motor skills (Seiler, 2010; Denadai et al., 2017). Based on this view we predicted that experts might indicate an activity decrease in areas relevant to the motor decision process. The opposite hypothesis was that there was no significant difference in brain activation between experts and novices when performing decision-making tasks.

MATERIALS AND METHODS

Literature Search

This ALE meta-analysis has been conducted following a strict protocol by using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

A literature search was conducted by PubMed,[1] ISI Web of Science,[2] Elsevier[3] and Cochrane Library.[4] All included articles were published in the English language until March 2021. The following search keywords were used: "athlete" OR "expert" OR "novice" OR "non-athlete," "decision-making" OR "decision," "functional magnetic resonance imaging" OR "fMRI" OR "positron emission computed tomography" OR "PET." The retrieval formula was ("athlete" [Mesh Terms] OR expert OR novice OR non-athlete) AND ("decision-making" [Mesh Terms] OR decision) AND ("functional magnetic resonance imaging" [Mesh Terms] OR "fMRI" [Mesh Terms] OR "positron emission computed tomography" [Mesh Terms] OR PET).

The titles and abstracts were independently screened by two trained reviewers (YD and LXH). Two independent reviewers completed the entire article inclusion process, and only articles that both reviewers reached an agreement on were finally included. When two independent reviewers disagreed on whether to include articles, resolved the differences through discussion, and seed the assistance of a third reviewer (DBL) if they still could not be resolved.

Inclusion and Exclusion Criteria

We selected studies considering the following inclusion criteria: (1) the samples included a group motor expert and a group novice; (2) motor experts with extensive experience were awarded the title of experts by their country, region, or school; (3) subjects performed motor decision-making task stimulus; (4) study with fMRI or PET; (5) the peak coordinates of brain activation areas were explicitly reported of motor experts and novices; (6) the reported results of activated foci were normalized to the Montreal Neurological Institute (MNI) (Collins et al., 1994) or the Talairach standardized stereotactic spaces (Paus et al., 1996); (7) whole-brain voxel analysis or at least one whole-brain analysis was performed; (8) subjects were healthy; (9) subjects were adults; (10) the language of studies was limited to English; (11) original research articles.

Exclusion criteria: (1) report coordinates were incomplete, or complete results have not been obtained after contacting the corresponding author; (2) research published in the form of conference reports, abstracts, etc.

These criteria identified 10 studies including 350 people (168 experts and 182 novices, 411 activation foci). **Figure 1** shows the outcomes of the search process.

[1]https://pubmed.ncbi.nlm.nih.gov/
[2]http://isiknowledge.com/wos
[3]https://www.elsevier.com/zh-cn
[4]https://www.cochranelibrary.com/

Data Extraction

The two reviewers (YD and LXH) extracted the following information from each included study: authors, age, year of publication, study name, type of coordinates, brain analysis method, number of participants, the ratio of male to female participants, comparison conditions, handedness, Foci.

Activation Likelihood Estimation Meta-Analysis

ALE is a quantitative meta-analysis method that uses a spatial variance model (3D Gaussian) to calculate the likelihood of each voxel being activated under a certain condition, thus obtaining the consistency of brain activation across multiple experiments (Laird et al., 2005; Eickhoff et al., 2009). Data processing was performed using GingerALE software (version 3.0.2)[5] (Eickhoff et al., 2012). The difference in coordinate space (MNI vs. Talairach space) could be explained by converting the coordinates in Talairach to MNI space using icbm2tal in GingerALE (Lancaster et al., 2007). Finally, all activation coordinates were displayed in MNI space. We adopted a threshold for the map of the final ALE score graph with a familywise error (FWE) at $p < 0.05$ and a minimum cluster size of $k > 10$ mm^3. For visualization, the ALE whole-brain maps were imported into Mango software (version 4.0.1)[6] overly on a standardized anatomical MNI template (Colin27_T1_seg_MNI) (Dehghan et al., 2016).

RESULTS

Study Selection and Characteristics

A total of 1,323 records were initially retrieved, and only 1,191 studies remained after deleting duplicates (n = 132). We screened potentially relevant articles by applying the inclusion and exclusion criteria (see **Supplementary Material 1**). Finally, 10 articles focusing on the brain activation of experts and novices while performing decision-making tasks were included in the present study. All included articles tested decisions made by experts and novices under the same stimuli. Among those papers, six (Wright et al., 2011; Wu et al., 2013; Balser et al., 2014; Wimshurst et al., 2016; Qiu et al., 2019; Blazhenets et al., 2021) determined the accuracy of the ball's flight direction, three (Bishop et al., 2013; Wright et al., 2013; Xu et al., 2016) tested to determine the accuracy of opponent behavior, one (Guo-Zheng, 2016) tested response accuracy rate of ball block. Regarding the types of sports including basketball, tennis, hockey, volleyball, handball, badminton, soccer, etc. **Table 1** described the detailed information of the included study.

Single Dataset Activation Likelihood Estimation Analysis Results

Experts had 93 foci in 5 different experiments, the 3 regions activated included the right inferior temporal gyrus (ITG)

[5]http://www.brainmap.org
[6]http://rii.uthscsa.edu/mango/

(BA 37), right sub-gyral (BA 37), right middle occipital gyrus (MOG) (BA 19).

Whereas novices had 124 foci in 7 different experiments. After completing the single data ALE analysis, novices activated the left precuneus (BA 7), left superior parietal lobule (SPL) (BA 7), left inferior parietal lobule (IPL) (BA 40), left middle frontal gyrus (MFG) (BA 6), left precentral gyrus (BA 4, BA 6), left cingulate gyrus (BA 24), left postcentral gyrus (BA 2), left supramarginal gyrus (BA 40), right middle temporal gyrus (MTG) (BA 37, BA 39), right superior temporal gyrus (STG) (BA22). **Table 2** and **Figure 2** showed the results of the single-dataset ALE analysis.

Dual Dataset Comparison Activation Likelihood Estimation Analysis

Experts did not have significant activation compared to novices. In contrast, novices were activated in the left middle temporal gyrus (MTG) (BA 19, BA 39), bilateral MOG (BA 18, BA 19), left posterior lobe, right lingual gyrus (BA 18), left precuneus (BA 31), right fusiform gyrus (BA 19), bilateral inferior occipital gyrus (IOG) (BA 17). **Table 2** and **Figure 3** showed the results of the ALE analysis for experts and novices comparisons.

DISCUSSION

The Effect of Handedness on the Results of Activation Likelihood Estimation Analysis

Handedness might affect an individual's skills and athletic performance (Raymond et al., 1996). Some studies also have found that handedness was associated with cognitive function (Buckingham et al., 2011; Somers et al., 2015). The results of an EEG study found that left-handed athletes had greater P300 wave amplitude than right-handed athletes, suggesting that left-handed athletes had an advantage in cognitive perception and observation, but slower processing than the right-handed athletes (Nakamoto and Mori, 2008). Almost all of the subjects in the existing fMRI literature of motor decision-making were right-handed since there were fewer left-handed athletes. Among the 10 articles included in this study, only one article did not report whether the subjects were right-handed or not (Wimshurst et al., 2016), and the remaining nine articles reported that the subjects were right-handed. Therefore, we considered the articles included in this study to be general.

Summary of Activation Likelihood Estimation Meta-Analysis Results

Through systematic review and ALE meta-analysis of the included papers investigating brain activation in decision-making tasks by experts and novices, we found that experts activated the right ITG, right sub-gyral, and right MOG, but novices activated more brain regions including the left middle temporal gyrus (MTG) (BA 19, BA 39), bilateral MOG (BA 18, BA 19), left posterior lobe, right lingual gyrus (BA 18), left supramarginal gyrus (BA 40), right fusiform gyrus (BA 19), bilateral inferior occipital gyrus (IOG) (BA 17). Results of this ALE meta-analysis showed significant clusters in novices, and they were located in the bilateral occipital lobe (including the MTG, MOG, IOG, lingual gyrus, fusiform gyrus, and precuneus), left posterior cerebellar lobe, and left MTG compared to experts. This also confirmed that long-term motor training could improve the neural efficiency of motor experts, reflecting the automated process of motor skills.

Brain Activation Contrasts Between Motor Experts and Novices in Decision-Making Tasks

There was substantial evidence that the occipital lobe played an important role in the processing of visuospatial information (Todorov and Sousa, 2017; Buening and Brown, 2018). Motor cognitive psychologists argued that decision-making was based on information, of which visual information was particularly important (Darren et al., 2016). The results of the present study showed that the occipital lobe had in novices compared to experts, suggesting that the brain required more visual information processing when performing decision-making tasks. The results also corroborated previous research (Jie, 2014; Filgueiras et al., 2017; Guo Z. et al., 2017; Blazhenets et al., 2021). When the brain was stimulated by complex motor scenarios, motor experts first transferred the stimulus information into the brain's perceptual system. The brain recognized the information and matched it with tactical information extracted from long-term memory and then made a final decision based on the learned motor skills (Smits et al., 2014). In contrast, novices performed the same task needing to find usable information and invalid information, which led to more visual information systems being activated to process and analyze information. Therefore, we believed that the primary mechanism for decreased activation in the expert's occipital lobe was that experts had higher neural efficiency, which implied task-specific brain function plus sparing (Neubauer and Fink, 2009; Ludyga et al., 2016). This suggested that visual information processing played a key role in motor decision-making behavior.

Compared with experts, the results of ALE analysis showed that novices activated the left posterior cerebellar lobe during the decision-making process. The cerebellar was more involved in motor regulating and motor learning (Ashida et al., 2019; Schmahmann et al., 2019). Several studies have indicated that the activation of the cerebellum during performing decision-making tasks could enhance decision-making planning, initiation, and control (Yarrow et al., 2009; Nowrangi et al., 2014; Kim et al., 2015). Previous studies have found that long-term professional motor training could alter cerebellar activation. For example, a study comparing brain activation in elite archers and non-archers during archery found that non-archers had more cerebellar activation than elite archers (Chang et al., 2011), which was consistent with the findings of Guo Z. et al. (2017). Authors indicated that experts through years of sports skill learning and training might develop precise and professional sports skills, which included the ability to rapidly regulate motor information and motor learning, whereas novices did not have the ability. Imamizu et al. (2000) suggested that motor could be accurately

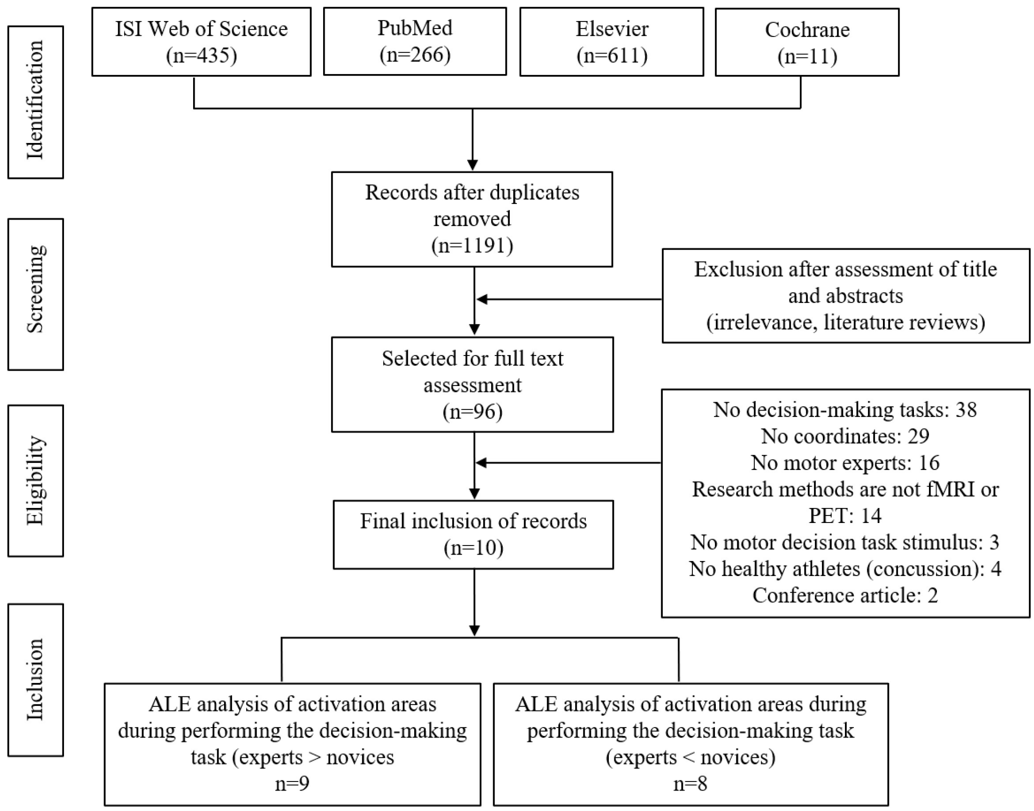

FIGURE 1 | Flowchart describing the process of study selection.

TABLE 1 | Basic information included literature.

References	Sample size	Imaging method	Expertise	Gender M/F	Space	Conditions	Handedness	Foci
Wu et al. (2013)	30	fMRI	Basketball	30/0	Talairach	Free-throw direction decision accuracy	Right	55
Balser et al. (2014)	32	fMRI	Tennis	16/16	MNI	Tennis flight direction decision	Right	22
Wimshurst et al. (2016)	30	fMRI	Hockey	19/11	MNI	Determine the accuracy of hockey hitting direction	/	76
Guo-Zheng (2016)	40	fMRI	Volleyball	20/20	MNI	The response accuracy rate of ball block	Right	38
Qiu et al. (2019)	47	fMRI	Basketball	47/0	MNI	Determines the direction and strength of the ball	Right	5
Blazhenets et al. (2021)	48	PET	Handball	48/0	MNI	Free-throw decision	Right	21
Xu et al. (2016)	34	fMRI	Badminton	19/15	MNI	Determines the direction and gender of the players	Right	24
Wright et al. (2011)	16	fMRI	Badminton	16/0	MNI	Decide where to drop the badminton	Right	50
Wright et al. (2013)	34	fMRI	Soccer	34/0	MNI	Decide the move direction in the opponent	Right	110
Bishop et al. (2013)	39	fMRI	Soccer	39/0	MNI	Decide an oncoming opponent's movements	Right	10

controlled by using internal models of the body and that after the cerebellum acquired internal models through long-term motor training, athletes were able to perform tasks in a relatively automated, energy-conserving processing mode. Based on this view we believed that the reduced activation of the expert cerebellum was due to the formation of internal models of the cerebellum.

The MTG (BA 39) was already known to be significantly involved in cognitive functions such as motor planning and information processing (Guo L. et al., 2017; Xu et al., 2019). The results of this study found that the left MTG was activated when novices made decision-making in sports, which reflected the fact that experts did not need to activate more cognitive areas of the brain. Motor psychologists have suggested that cognitive mechanisms might be the main reason for the different decision-making levels between experts and novices (Dew et al., 2009). Experts with extensive motor experience could facilitate sports memory and attention, especially the ability to increase the depth of attention and reduce the waning of attentional information in complex motor scenarios. However, when novices made motor decisions in face of unfamiliar motor conditions, activation of the left MTG might be due to further processing of motor behavior

TABLE 2 | ALE meta-analysis results according to experts, novices, and contrasts.

Anatomical region	Cluster	BA	MNI coordinates			Volume	ALE value
			X	Y	Z	(mm^3)	($\times 10^3$)
Experts							
R ITG	1	37	50	–68	–2	8,976	12.03
		37	56	–68	4		9.23
		37	62	–58	–4		8.64
R sub-gyral		37	46	–64	6		18.37
R MOG		19	40	–66	12		10.11
Novices							
L Precuneus	1	7	–24	–58	55	7,744	9.06
		7	–22	–48	56		8.86
L SPL		7	–34	–46	56		17.97
L IPL		40	–46	–34	40		8.81
L supramarginal gyrus		40	–40	–42	42		8.56
L MFG	2	6	–24	–6	54	7,120	17.73
		6	–28	–4	46		10.09
L precentral gyrus		4	–34	–12	64		9.07
		4	–34	–20	68		8.79
		6	–38	–6	52		8.65
L cingulate gyrus		24	–16	2	46		9.28
L postcentral gyrus		2	–44	–28	64		7.72
R MTG	3	37	50	–62	8	6,504	14.29
		39	46	–60	12		14.27
R STG		22	46	–52	20		9.15
		22	54	–48	8		8.97
		22	62	–46	12		8.84
		22	66	–42	18		8.83
Experts > Novices							
–	–	–	–	–	–	–	–
Experts < Novices							
L MOG	1	18	–20	–90	–4	27,000	17.46
		18	–14	–96	18		10.70
		19	–44	–80	18		9.18
		19	–48	–74	10		9.04
		18	–30	–84	6		7.95
		18	–26	–86	14		7.20
		19	–40	–88	12		5.06
L MTG		19	–44	–80	24		9.14
		19	–48	–62	16		8.83
		39	–40	–58	8		8.72
L IOG		17	–16	–98	–8		10.36
L lingual gyrus		18	–16	–104	0		8.62
L posterior lobe			–26	–82	–16		9.61
L precuneus		31	–30	–72	24		7.90
R lingual gyrus	2	18	30	–98	0	11,240	10.32
		18	20	–96	–10		10.05
		18	24	–86	–6		9.70
		18	10	–88	2		7.22
R MOG		18	28	–94	6		10.05
		18	22	–88	–2		9.92
R fusiform gyrus		19	30	–88	–10		9.64
R IOG		17	26	–100	–4		8.79

ALE maps were computed at a familywise error (FWE) corrected threshold of $p < 0.05$, with a minimum cluster size of $k > 10\ mm^3$. BA, Brodmann area, L, left, R, right, superior parietal lobule, SPL, inferior parietal lobule, IPL, middle frontal gyrus, MFG, middle temporal gyrus, MTG, superior temporal gyrus, STG, inferior temporal gyrus, ITG, middle occipital gyrus, MOG, inferior occipital gyrus, IOG.

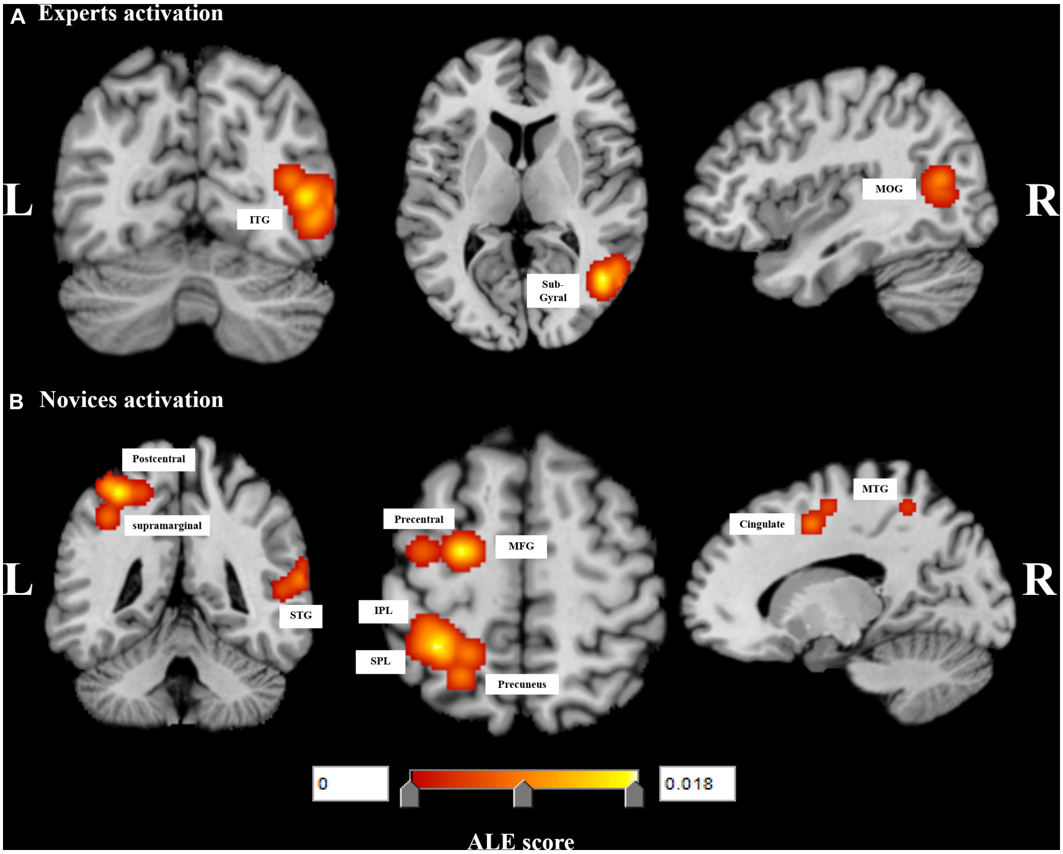

FIGURE 2 | Significant meta-analysis results for **(A)** experts and **(B)** novices performing decision-making tasks. L, left, R, right, inferior temporal gyrus, ITG, middle occipital gyrus, MOG, superior parietal lobule, SPL, inferior parietal lobule, IPL, middle frontal gyrus, MFG, middle temporal gyrus, MTG.

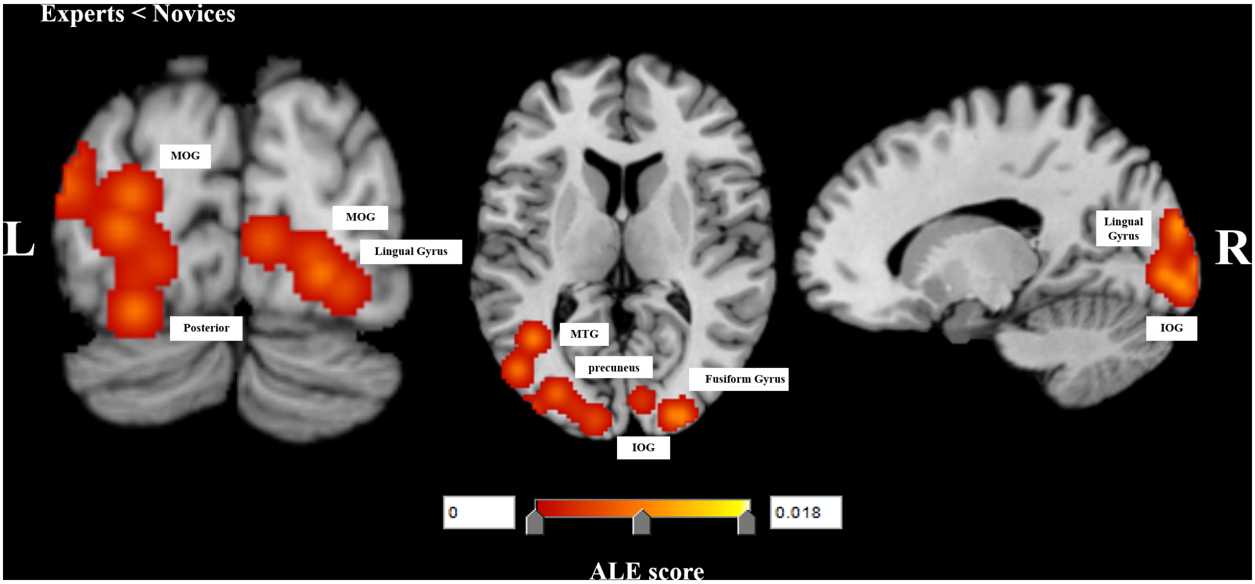

FIGURE 3 | Significant meta-analysis results for comparison between experts and novices performing decision-making tasks. L, left, R, right, middle temporal gyrus, MTG, middle occipital gyrus, MOG, inferior occipital gyrus, IOG.

information which reconfirmed the neural areas involved in motor information processing (Woods et al., 2014). Therefore, we argued that long-term motor training in athletes led to the more efficient cognitive neural network to adapt to the demands of high intensity and high correctness, which induced the brain to automatically process information. This was consistent with previous research findings (Babiloni et al., 2010; Zhang et al., 2019; Dobersek and Husselman, 2021).

Limitations and Future Research Directions

Potential limitations in this study should be mentioned. ALE analysis inevitably ignored the variation in each study and belonged to the statistical inference of fixed effects. Unlike a meta-analysis with complete activation maps, the data used in ALE were based on the reported data peak activation coordinates (Zhang et al., 2016). Therefore, it was unable to take into account studies without any significant categorical reporting, which might lead to systematic overestimation of biased results. Another limitation of this article was the gap between the designed motor situation and the real situation in included studies, which might make the findings not necessarily a true reflection of the actual movement, but rather an exploration of brain activation for decision-making tasks in a laboratory setting. Further development of realistic experimental designs or fMRI techniques could facilitate the direct exploration of decision-making in real motor situations, which was a direction of future research. Last, it was difficult to assess whether these activation regions were related to sports types due to the lack of comparisons between different motor experts, so further imaging studies were needed to compare brain activation alterations of different professional motor experts.

CONCLUSION

This study took a cognitive neuroscience perspective to reveal differences in the neural mechanisms underlying the motor decision-making processes of experts and novices. Our study provided new and meaningful evidence that greater activation for novices compared to experts in the bilateral occipital lobe, left posterior cerebellar lobe, and left MTG, but a decreased activation was not detected.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

DL was responsible for the conception and design of the study, explained the data results, and critically revised the manuscript. YD and LH performed the data acquisition and statistical analysis. YW completed the document screening and literature search. YD extracted the data and edited the manuscript. All authors participated in the study.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2022.854692/full#supplementary-material

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SYSTEMATIC REVIEW
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Effect of Exercise on the Cognitive Function of Older Patients With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Background: Aging and type 2 diabetes mellitus (T2DM) are important risk factors for the development of cognitive deterioration and dementia. The objective of this research was to investigate the effects of an exercise intervention on cognitive function in older T2DM patients.

Methods: Eight literature databases (PubMed, EBSCO, Scopus, Embase, The Cochrane Library, Web of Science, Ovid, and ProQuest) were searched from inception to 20 January 2022. The researchers examined randomized controlled trials (RCTs) that evaluated the impact of exercise on the cognitive performance of older T2DM patients. The Cochrane risk-of-bias tool (ROB 2) for RCTs was used to assess each study. The quality of evidence was assessed using the GRADE (grading of recommendations, assessment, development, and evaluations) approach. The mini-mental state examination (MMSE), Modified MMSE (3MSE), and Montreal cognitive assessment (MoCA) were used to evaluate the cognitive outcomes. We performed a subgroup analysis with stratification according to exercise intervention modality, duration, and cognitive impairment.

Results: Five trials were eligible, with a total of 738 T2DM patients. The combined findings revealed that exercise improved global cognitive function significantly (standardized mean difference: 1.34, 95% confidence interval: 0.23–2.44, $p < 0.01$). The effect of exercise on global cognitive performance was not significantly influenced by intervention modality, intervention duration, or cognitive impairment in the subgroup analysis ($p > 0.05$). In the studies that were included, no relevant adverse events were reported.

Conclusion: Exercise is beneficial in improving global cognitive function in older adults with T2DM. Studies with bigger sample sizes and higher quality are additionally expected to draw more definite conclusions.

Systematic Review Registration: [https://www.crd.york.ac.uk/PROSPERO/#recordDetails], identifier [CRD42022296049].

Keywords: exercise, type 2 diabetes mellitus, older adults, cognition function, meta-analysis

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INTRODUCTION

With changes in people's lifestyles and the aging population, the prevalence of diabetes has been increasing and is expected to increase to 783.2 million by 2045, but is even higher in older age groups (Sun et al., 2021). Type 2 diabetes mellitus (T2DM) represents 90–95% of all diabetes cases (American Diabetes Association, 2021). In the elderly population, diabetes leads to the onset of multimorbidity, polypharmacy, and disability, thus increasing the economic burden on society and patients' families (Salcedo Rocha et al., 2018). Global diabetes-related health spending is also estimated to increase from $966 billion in 2021 to $1,054 billion in 2045 (Sun et al., 2021).

Patients with T2DM are more likely to experience cognitive decline, which is more pronounced in older patients with T2DM, than those without the disease (Kotsani et al., 2018). However, cognitive dysfunction is often easily overlooked in patients with T2DM (Liu et al., 2020). Long-term chronic hyperglycemia can impair brain function and cause peripheral vascular complications such as neuropathy, stroke, and white matter lesions, which lead to cognitive dysfunction in patients with T2DM (Alosco et al., 2012; Luchsinger, 2012; Ho et al., 2013; Koekkoek et al., 2015). Cognitive impairment and dementia lead to reduced adherence to proper treatment for T2DM, which results in increased risks of complications such as cognitive dysfunction (Althubaity et al., 2021). This suggests that in patients with T2DM, the risk of cognitive deterioration can be reduced through well-controlled blood glucose levels (West et al., 2014).

Cognitive deterioration is more severe in older patients with T2DM and thus should be prevented or treated using effective measures. Exercise establishes a clinical treatment pathway for T2DM in primary care (Rehn et al., 2013; Rossen et al., 2015), and contributes to the reduction of the burden of chronic diseases and improvement of public health (Rossen et al., 2015). Many researchers have emphasized the relevance of physical activity for cognition, and the latest research suggests a positive association between exercise and all cognitive domains (Liu et al., 2021). Although some trials have shown exercise improves cognitive function in patients with T2DM, their results are inconsistent (Yanagawa et al., 2011; Espeland et al., 2017a; Chantre Leite et al., 2020; Molina-Sotomayor et al., 2020; Martínez-Velilla et al., 2021). One study found that 6 months of progressive aerobic and resistance training improved global and domain-specific cognitive function in patients with T2DM (Callisaya et al., 2017a). However, another study found that after 6 months of aerobic and resistance exercise with a lifestyle intervention, the cognitive function of patients with T2DM was negatively affected (Fiocco et al., 2013).

A meta-analysis of the influence of physical exercise on cognitive performance in diabetes patients that was published in 2021 uncovered that exercise improved cognitive function in patients. However, the interventions included in the study contained diet and exercise, not an exercise intervention alone, and the types of studies consisted of cohort studies and RCTs (Wang et al., 2021). Zhao et al. (2018) tried to systematically analyze the effects of physical exercise on cognitive function in people with T2DM, insulin resistance, or impaired glucose tolerance (IGT) in 2018. Their results indicated limited data supporting the idea that physical activity may enhance some cognitive functions in older adults with T2DM or IGT, but the effects were inconsistent. As the included studies include both observational and non-randomized controlled studies, further research is required. The question we wanted to investigate was whether exercise alone could improve cognitive function in older patients with type 2 diabetes.

The objective of this article was to systematically analyze the existing evidence from RCTs on the influence of regular physical activity on cognitive function in older T2DM patients. Thus this study reduces the uncertainty about the effects of exercise interventions on cognitive function in older patients with T2DM. It provides evidence for future non-pharmacological prevention and treatment methods for cognitive impairment in the older T2DM population.

MATERIALS AND METHODS

The analysis methodologies and eligibility criteria were set ahead of time and documented in a PROSPERO-registered protocol (CRD42022296049). The Preferred Reporting Items for Systematic Reviews and Meta-analyses were used in this meta-analysis (Page et al., 2021; **Supplementary Material**, PRISMA 2020 checklist).

Eligibility Criteria

The following criteria were used to determine whether or not trials should be included in this review. The study comprised older T2DM patients (aged 60 years and more). Participants could be male or female and from any country. Any structured exercise training program was completed for at least 8 weeks without the use of any additional treatment approaches or lifestyle changes. The fitness plans might be done anywhere (e.g., laboratory, home, or gym). Patients who did not receive contact/usual care were not on the waiting list, did not undertake a sham exercise or passive training, or did not receive an alternative active treatment were all eligible for comparison. To ascertain the outcome, any validated cognitive function test conducted at baseline and follow-up after exposure to an exercise intervention can be used. RCTs completed in humans were considered eligible for inclusion in the study. Conference proceedings, guidelines, dissertations, commentaries, reviews, animal model studies, and letters were all eliminated from consideration. Articles for which there was no full text or raw data were also eliminated. **Table 1** presents the PICOS criterion's inclusion and exclusion criteria.

Search Strategy and Study Selection Processing

Two review raters conducted a thorough literature search to find relevant articles (Y-HC and ZW). The search period covered the years from inception (1818～2004) to 20 January 2022. The following electronic databases were searched: PubMed, EBSCO, Scopus, Embase, The Cochrane Library, Web of Science, Ovid,

TABLE 1 | The inclusion and exclusion criteria under the PICOS criteria.

Parameter	Defined criteria for the present study
P (participants)	Older patients with T2DM (aged ≥ 60 years)
I (intervention)	Structured exercise for at least 8 weeks
C (comparison)	Standard care, waiting list, sham exercise, passive training, or active therapy options
O (outcomes)	Cognitive function
S (study design)	Randomized controlled trials

and ProQuest. No language or publication status restriction was set. The search keywords included "participant" (e.g., "diabetes mellitus, type 2"), "intervention" (e.g., "exercise"), and "outcomes" (e.g., "cognition," "executive," "attention," and "memory"). The description of the complete search strategy is provided in PDF (**Supplementary Material**, Database Search formula). We used the Mesh database for the PubMed search and combined Mesh terms with entry terms. After that, we made changes to other databases. Furthermore, the following filters were used: "randomized controlled trial" (publication kinds), "randomized" (title/abstract), and "placebo" (title/abstract). EndNote reference software (EndNote X9, Clarivate Analytics, Philadelphia, United States) was used to collate and save the trials, and duplicates were deleted. Two researchers (Y-HC and ZW) evaluated the titles and abstracts separately to select the papers that fit the criteria, and then read the entire texts to determine final eligibility. Until a consensus was reached, any disagreements amongst the study authors were handled through discussion or third-party consultation (L-YF or G-XN).

Data Extraction

All of the data was extracted and compiled independently by two researchers (Y-HC and ZW). We gathered the following details: (1) trial characteristics (lead author, year of publication, trial aim, trial design, inclusion/exclusion criteria, sample size, and allocation method); (2) participant characteristics (diabetes diagnosis, age, sex, BMI, length of diabetes diagnosis, and medication); (3) intervention (type, duration, frequency, and intensity); and (4) outcome measurements (all relevant cognitive outcomes and measurement tools). In the evaluation of the intervention effects at various time points, only the value obtained at the latest time point was taken into account. We contacted the authors to collect the original data if there was no relevant data in the paper. When the two reviewers couldn't agree, a third reviewer was brought in to help reach a conclusion (L-YF or G-XN).

Quality and Risk-of-Bias Assessment

Individual articles were evaluated separately by the two reviewers (Y-HC and ZW) using the Cochrane risk-of-bias tool for randomized trials (ROB 2), in accordance with Higgins et al.'s recommendations (Higgins et al., 2020). The questions in ROB 2 analyze five domains: the randomization procedure, deviations from the planned treatments, missing outcomes, outcome measurement, and reporting results selection. "Yes (Y)," "probably yes (PY)," "no (N)," "probably no (PN)," or "no information (NI)" was used to respond to the questions. The ROB 2 algorithm categorized bias risk as "low," "high," or "some concerns" at the conclusion of each domain. ROB 2 produced an overall rating after assessing the five domains. Publication bias could not be assessed because fewer than 10 studies were included. In addition, the GRADE (Grades of Recommendation Assessment, Development, and Evaluation) procedures were employed to assess the evidence quality (Guyatt et al., 2011). The GRADE system is a strategy for evaluating evidence quality based on the risk of bias, indirectness, inconsistency, imprecision, and publication bias. Evidence is rated as high, moderate, low, and very low in terms of quality. Disagreements between reviewers were addressed by additional discussion or, if necessary, by the involvement of a third reviewer (L-YF or G-XN).

Data Synthesis and Statistical Analysis

The meta-analysis was carried out using R Studio Version 4.1.2 software (RStudio, Boston, Massachusetts, United States), the R package used is "library(meta)." We gave a narrative overview of the results for outcomes that could not be aggregated. The standardized mean differences (SMDs) of pre- and post-interventions were computed and weighted by inverse variances, taking into account the various outcomes and units of cognitive measures utilized in the research. SMD, calculated as the mean difference (MD) divided by the standard deviation, was pooled in random-effects model in which weight of the study was determined by the D-L method (Borenstein et al., 2009). The SMD was Cohen's d, small, moderate, and high effect sizes were represented by Cohen's d values of 0.2, 0.5, and 0.8, respectively (Higgins and Green, 2011). Based on the assumption of varying genuine effect sizes (Higgins and Green, 2011), a random-effects model was utilized, which takes into account study variance and weighs each study appropriately. I^2 statistics and the Cochran Q test were used to determine heterogeneity. Small, medium and large quantities of heterogeneity are indicated by I^2 values of 25, 50, and 75%, respectively (Higgins and Green, 2011), or a p-value of ≥ 0.10 for the Q test (Higgins et al., 2003). Sensitivity analyses were carried out by removing studies one by one from the meta-analysis.

We pooled the total scores of the scales assessing global cognitive function (MMSE, 3MSE, and MoCA). The cognitive function of T2DM patients was assessed by the MMSE, 3MSE, and MoCA scales, and they were all high-merit indicators, with higher scores associated with better cognitive function. Due to the different scoring criteria, we used SMD for aggregation rather than MD. Some domain-specific cognitive functions, such as attention, executive function, and memory function, were not be aggregated. RCTs assessing the effects of exercise therapy on specific cognitive skills in older adults with T2DM were too few and inadequate to allow for a meta-analysis. Therefore, we did not perform aggregate analysis of these outcomes.

Subgroup analyses were conducted on the basis of categorical factors such as exercise intervention modality, intervention duration, and cognitive impairment to evaluate possible moderating effects. This study divided exercise intervention modalities into two categories: (Sun et al., 2021) single-mode exercise (aerobic or resistance exercise alone); and

(American Diabetes Association, 2021) multimodal exercise (aerobic exercise, resistance training, functional exercise, flexibility training, and balance training. Moreover, intervention duration (≥12 or <12 months) and cognitive impairment (with or without cognitive impairment).

RESULTS

Literature Search and Study Selection

The computerized database retrieval yielded a total of 5,069 entries. **Figure 1** depicts the study selection flowchart. A total of 2,045 duplicate entries were removed, while 2,987 irrelevant data were eliminated based on their titles and abstracts. Following that, 37 full-text papers were reviewed for eligibility, with 32 being rejected. The following were some of the reasons: Subjects' age does not match ($n = 3$), ongoing trial ($n = 24$); irrelevant outcome ($n = 2$); and no full text or data available ($n = 3$). Irrelevant outcome referred to outcome indicators for specific cognitive function domains, such as attention, executive function, and memory function.

Characteristics of the Included Studies

Finally, the final analysis comprised five studies with a total of 738 individuals, three of which were from various countries (Zhu et al., 2015; Espeland et al., 2017a; Yamamoto et al., 2021) (the United States, China, and Japan, respectively) and two from Spain (Molina-Sotomayor et al., 2020; Martinez-Velilla et al., 2021). **Table 2** lists the features of the studies that were included. The included literature was published from 2015 to 2021. The sample sizes for the research varied from 35 to 415 people. Two studies were conducted in aT2DM population without cognitive impairment (Espeland et al., 2017a; Yamamoto et al., 2021), two others on the T2DM population with cognitive impairment (Zhu et al., 2015; Molina-Sotomayor et al., 2020), and one study included T2DM populations with and without cognitive impairment (Martínez-Velilla et al., 2021). Among the included RCTs, four compared an exercise group with a non-exercise control group (Zhu et al., 2015; Molina-Sotomayor et al., 2020; Martínez-Velilla et al., 2021; Yamamoto et al., 2021) (e.g., maintained daily activities, education, and usual care), and only one compared exercise to gentle movements (Espeland et al., 2017a) (e.g., stretching and flexibility training). Two studies included aerobic activity, strength training, functional exercise, flexibility training, and balance training as part of a multimodal exercise design (Espeland et al., 2017a; Martínez-Velilla et al., 2021). Only aerobic (Zhu et al., 2015; Molina-Sotomayor et al., 2020) or resistance training were utilized in the remaining three trials (Yamamoto et al., 2021). The exercise intervention duration ranged from 3 to 24 months, and the exercise frequency varied from 3 to 7 sessions a week, lasting for 105–300 min/week. The duration of the exercise intervention protocols was <150 min/week in one study, <5 days/week in another study, and <12 months in two studies. Intervention modality, intervention duration, and cognitive impairment were all regarded as key confounding variables in the research. In none of the investigations, there were any adverse events linked to exercise.

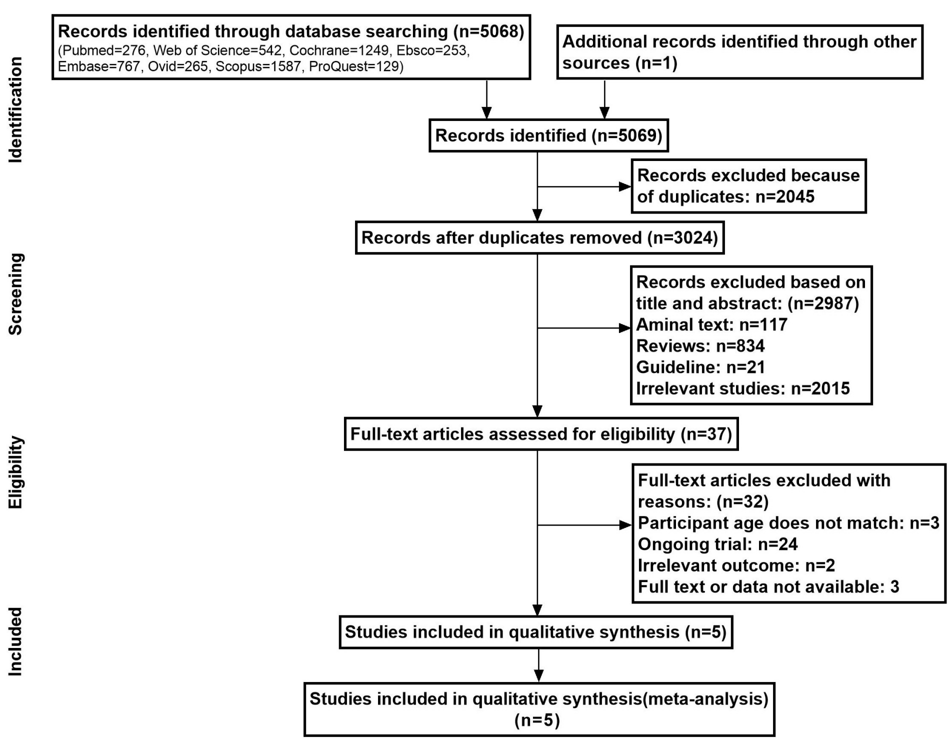

FIGURE 1 | Flow diagram of the literature search and article selection.

TABLE 2 | Characteristics of the included studies.

Author, year, country	Patients condition	Age range (years)	Sample (male/female)	Comparison	Intervention	Length (min/week)	Cognitive outcomes	Adverse event
Martínez-Velilla et al. (2021), Spain	T2DM	≥75	103 (50/53)	Usual care	Multimodal exercise, 40 min/day, 5–7 days/week for 3 months	200–280	Global cognition function/MMSE	None
Yamamoto et al. (2021), Japan	T2DM without cognitive impairment	70–79	35 (19/16)	Maintain daily activities	Bodyweight resistance and elastic band exercises, 15 min daily for 12 months	105	Global cognition function/MMSE	None
Molina-Sotomayor et al. (2020), Spain	T2DM with cognitive impairment	≥65	107 (0/107)	Maintained daily activities	Walking-based training, 60 min/day, 3 days/week for 6 months	180	Global cognition function/MMSE	None
Espeland et al. (2017a), United States	T2DM without cognitive impairment	70–89	415 (155/260)	Education workshops, stretching exercise, and flexibility training	Multimodal exercise, 50 min/day, 5–6 days/week for 24 months	250–300	Global cognition function/3MSE; processing speed/DSC-WAIS-III; memory function/HVLT-R; executive function/n-back task, TSP, EFT	None
Zhu et al. (2015), China	T2DM with cognitive impairment	≥60	78	Routine nursing	Baduanjin and routine nursing care, 40 min/day, 5 days/week for 12 months	200	Global cognition function/MoCA	None

MMSE, mini-mental state examination; 3MSE, modified mini-mental state examination; MoCA, Montreal cognitive assessment; DSC-WAIS-III, Digit Symbol Coding Test-Wechsler Adult Intelligence Scale, Third Edition; HVLT-R, Hopkins verbal learning test-revised; TSP, task switching paradigm; EFT, Eriksen flanker task.

Risk-of-Bias Assessment

Using the GRADE system, the included studies' methodological quality was rated as very low. **Figure 2** depicts the risk-of-bias plot and the author's assessment of the risk-of-bias items. Regarding the first criterion, the allocation sequences were randomized in all the included studies, but three studies did not specify whether allocation concealment was used (Espeland et al., 2017a; Molina-Sotomayor et al., 2020; Yamamoto et al., 2021). There are only two included studies that specifically describe randomization methods for RCTs, such as the random number table method and computer-generated random numbers (Zhu et al., 2015; Martínez-Velilla et al., 2021). None of the studies had missing baseline characteristics. In the research by Martínez-Velilla et al. (2021), we identified participants who moved to another group in both groups for departures from the targeted treatments. In the missing outcome data criteria, there was no risk of bias. Assessor blinding was not found in three trials when it came to outcome measurements (Zhu et al., 2015; Molina-Sotomayor et al., 2020; Yamamoto et al., 2021). In all the studies, the pre-specified analysis plans did not describe the statistical analysis methods and might confer potential risks, so we assigned "some concerns" in these studies.

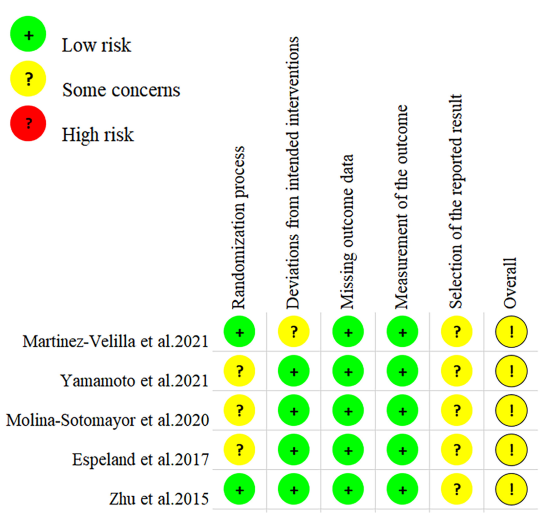

FIGURE 2 | Risks of bias of the included study according to the Cochrane Collaboration guidelines.

Synthesis of the Results (Global Cognitive Function)

The impact of physical exercise on global cognitive function in elderly patients with T2DM is shown in **Figure 3**. The effects of physical exercise on overall cognitive performance were assessed using the MMSE, 3MSE, and MoCA scales in five studies with a total of 738 individuals. The combined analysis demonstrated that exercise therapies had a significant impact on improving global cognitive function. However, heterogeneity among the studies was discovered [SMD = 1.34, 95% confidence interval (CI): 0.23–2.44, I^2 = 97%, $p < 0.01$]. The high heterogeneity of global cognitive function between research highlights the need of taking into account a variety of moderator variables when analyzing the effects of exercise.

Subgroup Analysis

Table 3 and **Figures 4–6** summarize the results of the subgroup analyses for global cognitive function. Subgroup analyses were

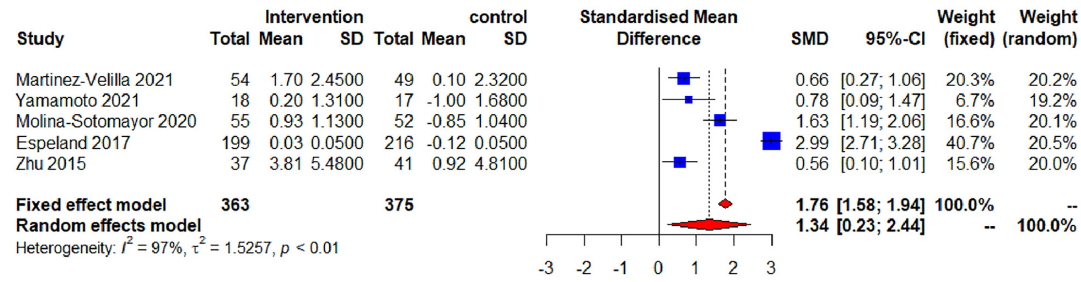

FIGURE 3 | Effectiveness of exercise for improving global cognitive function in the elderly.

TABLE 3 | Subgroup analysis for exercise and cognitive function.

Categorical moderator	Category	No. of studies	Cohen's *d*	95%CI	I^2%	Test of heterogeneity		
						Q	*d.f.*	*P* value
Modality	Multimodal exercise	2	1.83	−0.45 to 4.12	98.9%	0.47	1	0.49
	Single-mode exercise	3	1.00	0.28 to 1.72	82.9%			
Duration, month	≥12	3	1.46	−0.35 to 3.26	97.9%	0.09	1	0.76
	<12	2	1.14	0.20 to 2.08	90.1%			
Cognitive impairment	With cognitive impairment	2	1.09	0.05 to 2.14	90.9%	0.44	1	0.51
	Without cognitive impairment	2	1.91	−0.26 to 4.08	97%			

conducted based on the result of the five trials, which included exercise intervention modality and duration, as well as cognitive impairment, following a meta-analysis for global cognitive function. The impact of exercise on global cognitive performance was not significantly moderated by intervention modality, duration, or cognitive impairment in subgroup analyses.

Sensitivity Analysis

To analyze the impact of each study on the overall findings, a sensitivity analysis was undertaken utilizing the sequential omission of individual studies. The findings of the sensitivity analysis did not vary significantly when any studies were excluded, indicating that the results of the pooled effect (SMD) of the exercise interventions on cognitive performance were generally stable. **Figure 7** shows the results of the sensitivity analysis using the random-effects model.

DISCUSSION

This systematic review compiled evidence from recent RCTs and meta-analyzed the role of exercise on global cognitive function in older T2DM patients. The study demonstrates that exercise could significantly enhance global cognitive performance in older patients with T2DM. Unlike recently published studies (Zhao et al., 2018; Cooke et al., 2020; Wang et al., 2021), this study was an innovation in that the included studies were all RCTs that analyzed only the evidence of the impact of physical exercise on cognitive performance in older T2DM patients, controlling for some confounding factors of intervention modalities (e.g., diet, cognitive training, and lifestyle interventions) and populations.

Numerous studies have shown that exercise can promote neural regeneration and synaptogenesis in the hippocampus (Ma et al., 2017; De la Rosa et al., 2020), promote the release of neurotrophic factors (De la Rosa et al., 2020), reduce inflammatory processes (De la Rosa et al., 2020), and improve cognitive performance in different elderly populations. However, none of these recent meta-analyses systematically analyzed the impact of regular exercise on cognitive function in older patients with T2DM. Exercise's effects on cognitive function in patients with T2DM have been studied (Yanagawa et al., 2011; Fiocco et al., 2013; Chantre Leite et al., 2020; Molina-Sotomayor et al., 2020; Leischik et al., 2021), but the results vary. This study summarized the results of previously published articles and exhibited that long-term exercise regularly can improve global cognitive function (MMSE, 3MSE, and MoCA) in older adults with T2DM, which may lower the risk of complications and enhance the quality of life of patients to some extent. In the trials that were included, no adverse effects connected to exercise were recorded. As a result, regular physical activity may be safe and effective for enhancing cognitive function in elderly patients with T2DM.

The neurophysiological mechanisms of exercise as an adjunctive treatment modality for patients with T2DM that modulates cognitive processes are complex. Increasing growth factors and neuroplasticity, inhibiting inflammatory marker production, improving vascular function, and modulating the hypothalamic-pituitary-adrenal axis are the bases for exercise-induced cognitive improvement (Quigley et al., 2020). From another perspective, exercise improves overall cognitive function by inducing the release of the brain-derived neurotrophic factor (Rasmussen et al., 2009; Enette et al., 2017) and insulin-like growth factor 1 (Cassilhas et al., 2007)

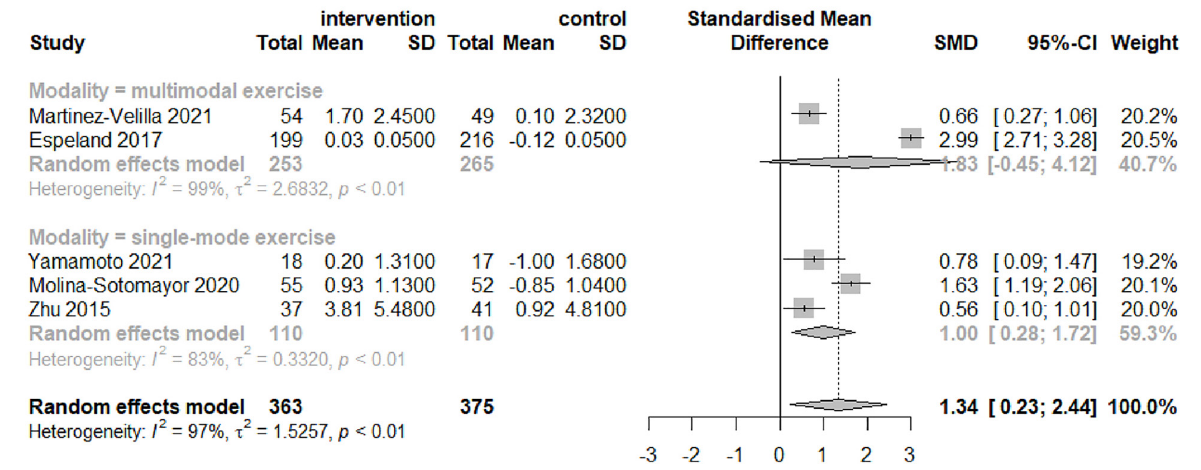

FIGURE 4 | Forest plot of the results of the subgroup analysis for intervention modality (multimodal and single-mode exercises) as a moderator.

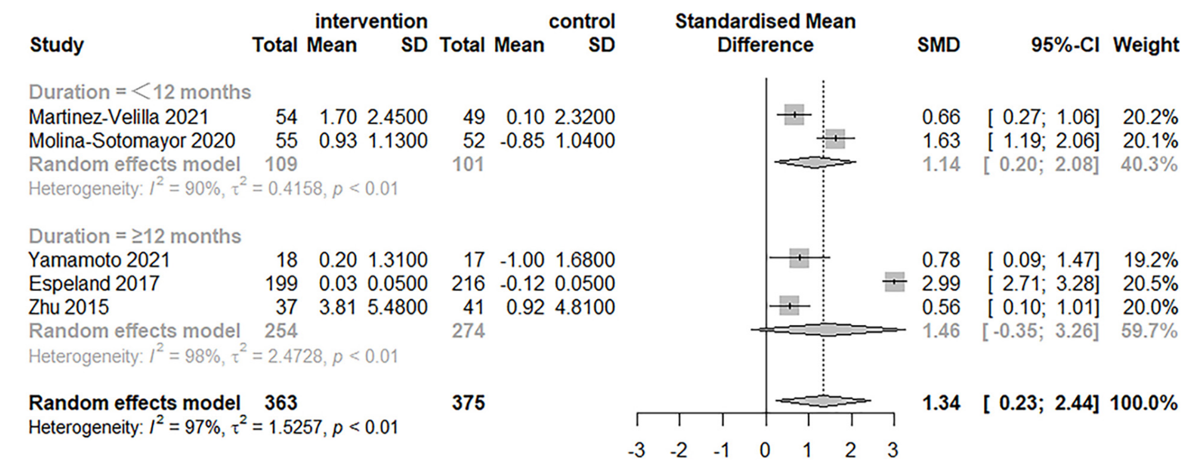

FIGURE 5 | Forest plot of the results of the subgroup analysis for duration as a moderator.

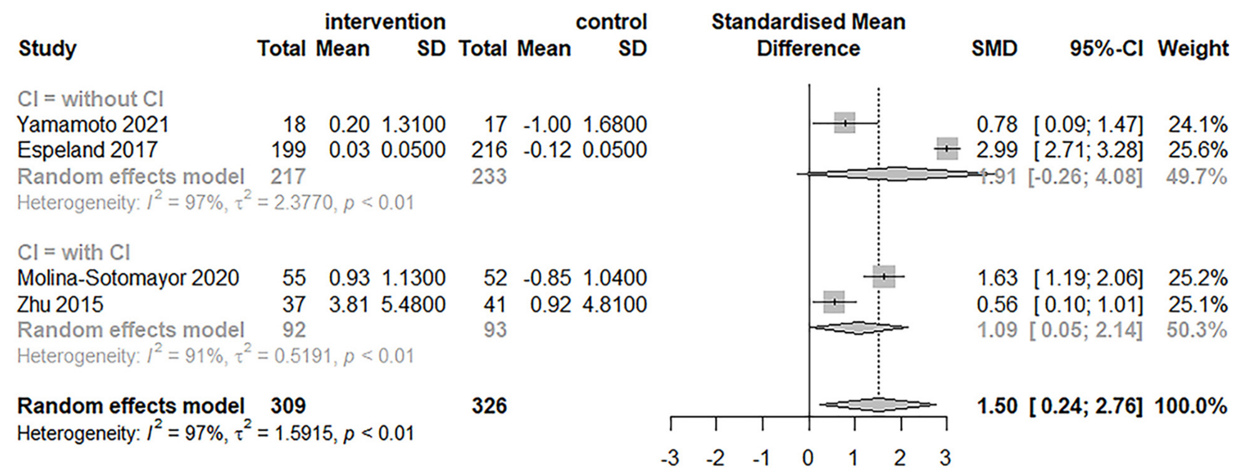

FIGURE 6 | Forest plot of the results of the subgroup analysis for cognitive impairment as a moderator.

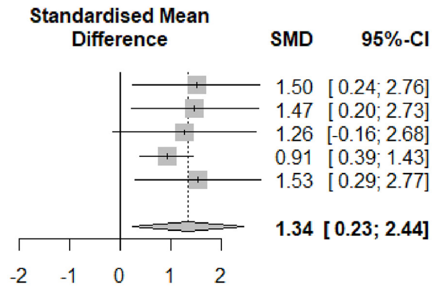

FIGURE 7 | Sensitivity analysis based on the random-effects model.

to promote structural and connectivity changes in the hippocampus, temporal lobe, frontal lobe, and corpus callosum (Erickson et al., 2009; Gomez-Pinilla and Hillman, 2013; Voss et al., 2013; Maass et al., 2016), which improve certain cognitive functions such as executive function, attention, processing speed, and memory, among other domain-specific cognitive functions, in older adults. In addition, maintaining excellent long-term glycemic management with exercise may minimize the risk of cognitive impairment.

Our study showed that exercise significantly improved global cognitive function and effectively reduced the cognitive impairment status in elderly patients with T2DM. In these patients, improving cognitive functional status can improve their self-management ability and treatment compliance, effectively prevent the occurrence and exacerbation of complications, and to some extent, improve their general health condition. Exercise is a simple and easy-to-learn therapy choice for T2DM that may be practiced in the community or at home. Moreover, it is a low-risk, low-cost therapeutic option with several physical and psychological advantages applicable to both primary care and hospitals.

We summarized other specific cognitive function domains included in the study (as shown in **Table 1**), such as processing speed (DSC-WAIS-III), memory function (HVLT-R), and executive function (n-back task, TSP, and EFT) because of the evidence that exercise can improve cognitive function in specific areas of the brain, such as attention, executive function, and memory function in patients with T2DM (Baker et al., 2010; Callisaya et al., 2017b; Espeland et al., 2017b). Unfortunately, RCTs evaluating the effects of exercise therapies on particular cognitive skills in older persons with T2DM are scarce and insufficient, making meta-analyses impossible.

The results of the subgroup analysis performed in this study showed that confounding factors such as the type and duration of exercise intervention as well as the existence of cognitive impairment had not significantly affected the improvement of global cognitive function by exercise. However, the impact of an exercise intervention on global cognitive function exhibited high heterogeneity, according to our data. In the subgroup analysis based on exercise type, multimodal exercise interventions were not better than single-exercise modalities in improving global cognitive function in older T2DM patients. This matches the findings of two previous meta-analyses, which showed that both single-aerobic exercise and aerobic exercise paired with additional exercise therapies helped diabetes patients improve cognitive function (Wang et al., 2021). The other meta-analysis of the improvement of cognitive performance by exercise in older adults by exercise showed the benefits of both aerobic and resistance training on cognitive function (Northey et al., 2018). However, some studies have shown more cognitive benefits of multi-component exercise interventions such as aerobic, resistance, balance, and flexibility training in healthy older adults, especially when combining aerobic and resistance exercises (Colcombe and Kramer, 2003; Kramer and Colcombe, 2018). It has been shown that there is a significant positive correlation between balance function and cognitive function, and that older adults with poor balance are at greater risk for impaired cognitive function (Meunier et al., 2021). Cognitive decline in older adults can be prevented through exercise prescriptions that include balance training. In addition, regular aerobic walking training outdoors can improve cognitive function by allowing older adults to maintain greater balance in their bodies (Battaglia et al., 2020). All of these exercise modalities have been shown to improve cognitive function in older adults. There is some ambiguity in the choice of exercise intervention methods, which may be related to the specific populations, settings, and intervention duration of the different studies. Therefore, further research is needed in this area. In addition, there was disagreement about the duration of the intervention. In our research, intervention duration does not constitute a confounding factor affecting intervention outcomes. This is consistent with the results of another meta-analysis, where the total duration of the intervention and the weekly exercise intervention hours did not significantly affect cognitive function in older adults (Sanders et al., 2019). However, some meta-analysis showed that long hours of exercise per week tended to be associated with improved cognitive performance (Firth et al., 2017), and there is also evidence to support that structured, longer duration, and multimodal exercise intervention programs can better improve cognitive performance and overall function in older adults (Kirk-Sanchez and McGough, 2014). Longer exercises durations may result in greater cognitive benefits for older adults (Hewston et al., 2021). The reasons for these differences may be due to the large variation in the total weekly intervention duration, frequency, and intensity of the exercise program across the different studies included. Another possible reason for the results is that the number of included studies was small and the subgroup analysis was more confounded by random errors. Further studies are needed regarding the dose-effect of exercise prescription on cognitive function in elderly patients with T2DM. A Cochrane review and an RCT found that exercise had no benefit for cognitively healthy older adults (Sink et al., 2015; Young et al., 2015). However, we performed a subgroup analysis based on the presence or absence of cognitive impairment and found that exercise interventions were beneficial for both older patients with T2DM with and without cognitive impairment, with no significant differences. Previous systematic reviews have also supported the effectiveness of physical activity on cognitive performance in older adults with and without cognitive impairment (Northey et al., 2018; Falck et al., 2019), such as healthy individuals (Sáez de Asteasu et al., 2017), individuals with mild cognitive impairment (Song et al., 2018), and individuals with dementia (Groot et al., 2016; Jia et al., 2019). This suggests that exercise not only improves cognitive function (Ludyga et al., 2016; Falck et al., 2019), but also prevents (Bherer et al., 2013) and reduces cognitive decline (Musich et al., 2017).

This study has several limitations that might have affected its conclusions and significance. First, just five experiments with a modest number of samples were combined. Second, the methodological quality of the included studies was assessed as "very low" using the GRADE method. Third, because the included studies used different cognitive assessment scales, this might have led to the significant heterogeneity of the results. Despite these limitations, our findings still have some implications.

The current study's main strength is that it provides an updated summary of RCTs of the effects of regular exercise on cognitive function in elderly patients with T2DM, which implies prospective observations and a causal rationale. Second, we excluded a large number of studies in which exercise was used as an adjunctive component of another intervention, such as cognitive training combined with exercise (Shellington et al., 2018) and diet combined with exercise training (Rapp et al., 2017; Espeland et al., 2018), and included only studies in which exercise was the only intervention. The findings of this research imply that the improvement of cognitive function by exercise in elderly patients with T2DM is practical and generalizable. To our knowledge, this is the first research to examine the effects of exercise on cognitive performance in older people with T2DM using a systematic review and meta-analysis. As a consequence, the findings of this research might be used as a recommendation for the implementation of exercise in the senior T2DM patient population.

Furthermore, only a few original articles have been published on the effects of physical exercise on specific domains of cognitive function such as executive function, attention, and memory in elderly patients with T2DM. Thus, further research is needed. Future research should expand intervention protocols and cognitive assessment areas, improve the research quality, and investigate the effects of various types of exercise modalities on physical inactivity and cognitive impairment in older adults with T2DM to develop a healthy lifestyle and exercise prescription recommendations to prevent the onset of dementia.

CONCLUSION

The result of the systematic reviews and meta-analyses performed in this study suggest that both single-modal and multimodal exercise regularly for >3 months can enhance global cognitive function in older patients with T2DM, regardless of cognitive impairment. However, with the limited inclusion and considerable heterogeneity of the studies included, this finding should be treated with caution. To give further evidence, more RCTs implementing standardized study designs are required. Exercise's impact on specific cognitive function domains in older patients with T2DM should also be investigated.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

Y-HC and ZW conceived and designed the study, carried out the literature searches, extracted the data, and wrote the manuscript. Y-HC, ZW, and L-YF assessed the study quality and performed the statistical analysis. G-XN revised the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2022.876935/full#supplementary-material

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Change in Latent Gray-Matter Structural Integrity Is Associated With Change in Cardiovascular Fitness in Older Adults Who Engage in At-Home Aerobic Exercise

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In aging humans, aerobic exercise interventions have been found to be associated with more positive or less negative changes in frontal and temporal brain areas, such as the anterior cingulate cortex (ACC) and hippocampus, relative to no-exercise control conditions. However, individual measures such as gray-matter (GM) probability may afford less reliable and valid conclusions about maintenance or losses in structural brain integrity than a latent construct based on multiple indicators. Here, we established a latent factor of GM structural integrity based on GM probability assessed by voxel-based morphometry, magnetization transfer saturation, and mean diffusivity. Based on this latent factor, we investigated changes in structural brain integrity during a six-month exercise intervention in brain regions previously reported in studies using volumetric approaches. Seventy-five healthy, previously sedentary older adults aged 63–76 years completed an at-home intervention study in either an exercise group (EG; n = 40) or in an active control group (ACG; n = 35). Measures of peak oxygen uptake (VO_2peak) taken before and after the intervention revealed a time-by-group interaction, with positive average change in the EG and no reliable mean change in the ACG. Significant group differences in structural brain integrity changes were observed in the right and left ACC, right posterior cingulate cortex (PCC), and left juxtapositional lobule cortex (JLC). In all instances, average changes in the EG did not differ reliably from zero, whereas average changes in the ACG were negative, pointing to maintenance of structural brain integrity in the EG, and to losses in the ACG. Significant individual differences in change were observed for right ACC and left JLC. Following up on these differences, we found that exercising participants with greater fitness gains also showed more positive changes in structural integrity. We discuss the benefits and limitations of a latent-factor approach to changes in structural brain integrity, and conclude that aerobic fitness interventions are likely to contribute to brain maintenance in old age.

Keywords: physical activity, fitness, brain structure integrity, aging, older adults, structural equation modeling

INTRODUCTION

As a result of progress in global health and development, the worldwide population of individuals over 60 years old is projected to double by 2050 (HelpAge International, 2018). However, as the proportion of older adults in the population increases, so does the concern of health-related changes associated with advancing adult age. Brain health is of great societal importance, as the risk of cognitive impairments leading to dementia increases with age, and individual differences in the degree to which brain structure, function, and neurochemistry can be maintained into old age are hypothesized to predict individual differences in cognitive functioning among older adults (Nyberg et al., 2012; Lindenberger, 2014; Cabeza et al., 2018; Nyberg and Pudas, 2019; Nyberg and Lindenberger, 2020; Johansson et al., 2022).

Aerobic exercise shows promise as a modifiable lifestyle factor that may potentially promote brain maintenance in old age. Intervention studies focusing on volumetric characteristics of brain structure have found that gray-matter (GM) volume shows more positive changes in exercisers than control participants in frontal areas, such as the anterior cingulate cortex (ACC), and in temporal areas, such as the hippocampus (Colcombe et al., 2004; Erickson et al., 2011). Higher levels of and more positive changes in physical fitness have also been associated with greater GM volume and attenuation of volume loss in prefrontal, parietal, and temporal regions, including the hippocampus (Colcombe et al., 2003; Weinstein et al., 2012; Maass et al., 2015; Kleemeyer et al., 2016).

However, individual measures such as GM probability may afford less valid conclusions about maintenance or losses in structural brain integrity on a generalized level than a latent construct based on multiple indicators. Latent constructs express the variance shared by multiple measures, thereby separating common variance from specific variance and measurement error (Wansbeek and Meijer, 2001). Therefore, the use of latent factors can improve the estimation of associations among constructs of interest. Based on pioneering work by Kühn et al. (2017), Köhncke et al. (2021) introduced a multi-trait multi-method model using structural equation modeling (SEM) capturing the shared variance between GM volume, mean diffusivity (MD), and magnetization transfer (MT) ratio in a latent factor of GM structural integrity for several regions of the brain. The authors were able to show that, in a cross-sectional sample, older participants generally showed lower scores on these integrity factors, which they interpreted as a reflection of age-related deterioration of overall GM, in line with studies focusing on single indicators (Raz et al., 2005; Fjell and Walhovd, 2010; Grydeland et al., 2013; Seiler et al., 2014). In addition, GM structural integrity correlated positively with episodic memory performance (Köhncke et al., 2021).

In the current intervention study, we adapted this cross-sectional model of GM structural integrity to a longitudinal context in order to measure change in structural integrity as a latent factor in brain regions of interest previously reported in studies using volumetric approaches. The three indicators used in the current model were all measured using magnetic resonance imaging (MRI) and captured different characteristics of GM structural integrity. GM volume was calculated using T_1-weighted images and voxel-based morphometry (VBM; Ashburner and Friston, 2000; Good et al., 2001), which estimates GM concentrations at each voxel based on signal intensity. MT saturation, an improvement to the MT ratio measure, which is affected by spatial variations of the transmit field for excitation and the local T_1 relaxation (Helms et al., 2008b), was used in the current models. MT maps quantify the transfer of magnetization between tissue water and protons bound to macromolecules, and can be used to assess microstructural changes to GM, with lower MT values correlating with demyelination and axonal loss (see Seiler et al., 2014). MD, measured using diffusion-weighted imaging (DWI), estimates the rate of water diffusion in each voxel (Pierpaoli and Basser, 1996), and is commonly used as a measure of white matter integrity, but can also be used as an index of GM density, with greater MD values corresponding to lower tissue density, likely reflecting demyelination (Song et al., 2005) and lower axon fiber density (Beaulieu, 2002; Fukutomi et al., 2019). By combining these three imaging modalities, we established a latent factor of GM structural integrity representing the commonalities across these three measures of brain structure. We use this novel longitudinal modeling approach to look at exercise-induced changes in a latent factor that represents general structural integrity, focusing on the shared variance of GM volume, MT, and MD, rather than any one of these alone, thereby removing any modality-specific measurement error. Given this emphasis on the commonalities across the individual modalities and to acknowledge the level of abstractness of this latent factor, we refer to this factor as "integrity."

The AKTIV Study

Previous studies investigating the effects of exercise among older adults generally have been conducted in a laboratory setting (e.g., Colcombe et al., 2006; Erickson et al., 2011), which may not reflect the exercise opportunities accessible to most older adults in their everyday lives. To examine whether engaging in aerobic exercise at home may also benefit older adults in terms of both fitness and brain health, the "Aktives Altern für Körper und Geist" (active aging for body and mind) study (AKTIV) implemented a personalized at-home physical exercise regime.

In the current analyses, we first investigated whether six months of moderate, at-home aerobic exercise could effectively boost cardiovascular fitness in older adults. We then validated the GM structural integrity model in a longitudinal manner in 12 regions of interest (ROIs) in the frontal, midline, and temporal areas selected based on previous publications (Colcombe et al., 2006; Erickson et al., 2011), and examined whether the group who exercised showed either gains (increase over controls) or maintenance (attenuation of loss relative to controls) in GM structural integrity within these regions. Finally, we investigated the association between changes in cardiovascular fitness and changes in structural brain integrity, with the hypothesis that greater increases in fitness should be positively associated with greater increases (or smaller losses) in GM structural integrity.

MATERIALS AND METHODS

Sample and Study Design

In the current analyses, we focused on the effects of physical training on GM structural integrity by comparing a group of individuals who regularly engaged in aerobic exercise with a group of sedentary individuals. These two groups were drawn from the larger AKTIV study, which investigated the effects of cognitive and physical training in comparison to an active control group (ACG). Here, we explored the effects of physical training alone vs. no physical training (see Interventions for details) with a sub-sample of 75 healthy, previously sedentary adults aged 63–76 years.

A full description of the AKTIV study design and methods can be found in Wenger et al. (2022); for convenience, we describe relevant materials and methods here. Volunteers for the AKTIV study were recruited through a participant data bank with participants from earlier, unrelated studies, and newspaper advertisements. A telephone screening was conducted to exclude individuals if they met any of the following criteria: MRI contraindications; inability to meet the time requirements of the study; not right-handed; younger than 63 or older than 78 years old at the start of the study; already engaging in aerobic exercise more than once every 2 weeks; fluent in a language other than German or English, or fluent in more than two languages; receiving medical treatment for Parkinson's, gout, rheumatism, heart attack, stroke, cancer, severe back problems, severe arrhythmia, severe chronic liver or kidney failure, severe disease of the hematopoietic system, mental illness (e.g., depression), or neurological disease (e.g., epilepsy, brain tumor). The 201 volunteers who did not meet the exclusion criteria were randomly assigned (with the exception of couples who were jointly assigned so that participants would remain blind to other groups) to one of four groups: (1) an ACG, (2) a language training group, (3) a physical exercise training group, or (4) a combined language and physical exercise training group. Next, potential participants were invited to a physical assessment including cardiopulmonary exercise testing (CPET) with lactate diagnostics at the Department of Sports Medicine at the Charité – Berlin University of Medicine. Based on this exam, a further 22 volunteers dropped out or were excluded due to existing medical conditions. Finally, participants underwent an initial MRI session before beginning their assigned training [pre-intervention, time point 1 (T1)]. Nineteen participants dropped out before the training started due to disinterest and one additional participant was excluded due to claustrophobia. Thus, the effective initial sample consisted of 159 individuals.

After 3 months of training [mid-intervention, time point 2 (T2)], MRI acquisitions were repeated, consisting of the same scans. After a total of 6 months of training [post-intervention, time point 3 (T3)], MR measures were acquired once more, and participants again underwent CPET at the Charité.

During the intervention, 17 participants dropped out due to physical complaints (e.g., knee or back pain during training), disinterest, time constraints, or unspecified reasons.

The Ethics Committee of the German Psychological Society (DGPs) approved the study and written informed consent was collected from all participants.

Interventions

As previously stated, we focused on the effects of physical exercise and therefore only used the data of participants who completed the intervention in the exercise-only group or the ACG.

Participants in the exercise group (EG; n = 40 completed, mean age = 69.8 years, 50% females) engaged in moderate at-home exercise three to four times per week at any time of the day using a bicycle ergometer (DKN Ergometer AM-50) and a personalized interval training regime programmed onto tablets (Lenovo TB2-X30L TAB) that were synced to the ergometers *via* Bluetooth. Tablets were equipped with SIM cards so that data could be uploaded to the study server whenever an Internet connection was available. The training initially lasted 30 min at an individually set intensity (25–140 W, mean = 67.9, SD = 26.65). After completing each training session, participants could indicate if they found the training too easy or too difficult, and the intensity could be remotely adjusted accordingly. In this way, the training was highly personalized so that participants would not be discouraged by an exceedingly easy/difficult exercise program. Approximately every two weeks, difficulty was automatically increased by 3 min per interval (up to 56 min total) and 3–4 W. Participants in the EG were also instructed to read pre-selected literature on the tablet at a slow pace for an additional 15 min on days when they trained and for 45 min on the other days, so that participants in both groups would engage in approximately 45 min of study-related activity on at least six days per week. Finally, those in the EG participated in weekly 1-h group sessions (5–10 participants per session) at the institute consisting of toning and stretching, led by an external instructor.

Participants in the ACG (n = 35 completed, mean age = 70.7 years, 40% females) also received a tablet and were instructed to read pre-selected literature for 45 min daily for at least six days per week. These participants also attended weekly group sessions during which they discussed literary excerpts led by external facilitators.[1]

Compliance was defined as engaging in at least an average of 90 min of group-relevant activity (reading or exercise) per week over 21 weeks (≥1890 min; $n_{non\text{-}compliant}$ in ACG = 3, $n_{non\text{-}compliant}$ in EG = 4) with no pauses of longer than 2 weeks ($n_{non\text{-}compliant}$ in EG = 1). Participants in the EG also needed to exercise at a steady or slightly increasing intensity (based on Watts) over the duration of the intervention, meaning those with decreasing Wattage were counted as non-compliant ($n_{non\text{-}compliant}$ in EG = 5).

Finally, regarding sample size, *post hoc* sensitivity analyses conducted in G*Power (version 3.1.9.6; Faul et al., 2007, 2009) indicated that, with $\alpha = 0.05$, $1 - \beta = 0.95$, and a study design with two groups and three time points, a sample size of $N = 75$ could reliably capture time-by-group interaction effects with an effect size of $f \geq 0.19$ and correlations with a coefficient of $r \geq 0.367$.

Data Acquisition

Cardiovascular Fitness

Cardiovascular fitness, indexed by peak oxygen uptake (VO_2peak; measured at 30-s intervals, relativized to body weight in kg), was assessed at the physical assessments at pre- and post-intervention using CPET. This was conducted under the supervision of the overseeing physician using a bicycle ergometer (Ergoselect 100k, Ergoline GmbH, Bitz, Germany) using the Quark Clinical-based Metabolic Cart with the standard Breath-by-Breath setup, and the V2 Mask (Hans Rudolph, Inc.), which covers the mouth and nose, and is fastened to the back of the head. Participants were instructed to pedal at a constant rate of 60–70 rotations per minute during the entire protocol, which consisted of a 3-min rest phase, an exertion phase with a starting resistance of 20 W, which increased by 20 W every 3 min until participants reported they had reached maximum exertion, and a 5-min recovery phase with no resistance.

Magnetic Resonance Imaging

Acquisition

Participants were scanned pre-, mid-, and post-intervention. MR images were acquired using a 3T Magnetom Tim Trio MRI scanner system (Siemens Medical Systems, Erlangen) using a 32-channel radiofrequency head coil. T_1-weighted images were obtained using a 3D T_1-weighted magnetization prepared gradient-echo (MPRAGE) sequence. The multi-parameter mapping protocol used to acquire the MT maps comprised one static magnetic (B_0) gradient echo (GRE)-field map, one radiofrequency (RF) transmit field map (B_1), and three multi-echo 3D fast low angle shot (FLASH) scans (Helms et al., 2008b; Tabelow et al., 2019). Diffusion-weighted images were obtained with a single-shot diffusion-weighted spin-echo-refocused echo-planar imaging sequence. Further details regarding the acquisition parameters can be found in the **Supplementary Material**.

[1]http://shared-reading.de/

Preprocessing

Structural T_1-weighted images were preprocessed using the Computational Anatomy Toolbox 12 (CAT12, Structural Brain Mapping group, Jena University Hospital; Gaser and Dahnke, 2016) in Statistical Parametric Mapping (SPM12, Institute of Neurology[2]) using the default parameters of the longitudinal pipeline. Estimation of MT maps was conducted in SPM12 using an adapted longitudinal pipeline with the hMRI toolbox (Tabelow et al., 2019[3]). DW images were preprocessed using MRtrix (version 3.0_RC3; Tournier et al., 2019), FSL (FMRIB's Software Library, version 6.0.2; Smith et al., 2004; Woolrich et al., 2009; Jenkinson et al., 2012), and ANTS (version 2.2.0; Avants et al., 2010, 2011), following the Basic and Advanced Tractography with MRtrix for All Neurophiles (B.A.T.M.A.N.) tutorial (Tahedl, 2018). Further details regarding preprocessing can be found in the **Supplementary Material**.

Regions of Interest

Regions of interest were selected based on previous intervention studies on the effects of aerobic exercise on brain structure (Colcombe et al., 2006; Erickson et al., 2011). Mean values of VBM, MT, and MD were extracted from the left and right hippocampus, ACC, posterior cingulate cortex (PCC), precentral gyrus (PCG), juxtapositional lobule cortex [JLC, previously supplementary motor cortex (SMA)], and pars triangularis and pars opercularis combined as inferior frontal gyrus (IFG), as defined by the Harvard–Oxford cortical and subcortical structural atlases[4,5] (Desikan et al., 2006), for a total of 12 ROIs. VBM and MT maps were calculated such that each participant's resulting map was in MNI space, so ROI masks were simply resized using the *Coregister and reslice* module in SPM12 with the first participant's map at T1 as a reference, and *fslstats* in FSL was used to extract the mean and SD across all non-zero voxels within each ROI. As calculation of MD maps resulted in images in each participant's native space, ROI masks were first transformed into native space for each participant using *applywarp* in FSL with the transformations generated during preprocessing and used to transform the non-diffusion-weighted images into native space, then *fslstats* was used to extract means and SDs across all non-zero voxels.

VBM values from each ROI were adjusted for intracranial volume [ICV, calculated using the *Estimate TIV and global tissue volumes* module in CAT12] using the analysis of covariance formula from Raz et al. (2005): adjusted volume = raw volume $-$ b $\times$ (ICV $-$ mean ICV), where b is the slope of regression of GM probability in the relevant ROI on ICV.

Statistical Analyses

All statistical analyses were conducted using R (R Core Team, 2021), version 4.1.2 (2021-11-01), in RStudio (RStudio Team, 2021), version 2021.09.1.

[2]www.fil.ion.ucl.ac.uk/spm

[3]https://hmri-group.github.io/hMRI-toolbox/

[4]https://neurovault.org/images/1705/

[5]https://neurovault.org/images/1700/

Univariate and Multivariate Outlier Detection

Univariate outliers within each measure and time point were defined as data points further than 4 SD away from the mean, resulting in one data point being discarded (hippocampus MT at T3). Multivariate outlier detection was conducted within measures across all three time points (two time points for VO_2peak) for complete cases using *robustMD* from the faoutlier R package (Chalmers and Flora, 2015) with the classical product-moment method (criterion = 0.001). In this way, we looked for abnormal patterns across time points within our sample (e.g., one data point having a much higher value than the other two), and removed all three data points of such outliers. This resulted in no cases being discarded for VO_2peak, and 17 out of 2052 cases being discarded across the three MRI modalities and 12 ROIs in participants with all three observations.

Structural Equation Modeling

SEM was used to investigate differences in group means of change in cardiovascular fitness indexed by VO_2peak and latent GM integrity, as well as the relationship between these two changes using a multivariate, multigroup approach. Models were specified and estimated using the OpenMx R package (Pritikin et al., 2015; Neale et al., 2016; Hunter, 2018; Boker et al., 2021), version 2.19.8. Full information maximum likelihood (FIML) was used to account for missing data without the need for case-wise deletion. Observed variables were rescaled to have a mean of 0 and a SD of 1 longitudinally (i.e., data from all time points were first stacked then rescaled) to preserve the relative mean differences between the same indicators measured at different time points. The root mean square error of approximation (RMSEA) and the comparative fit index (CFI) were used to evaluate model fit, using rough thresholds of RMSEA < 0.08 and CFI > 0.90 to indicate acceptable model fit (Schermelleh-Engel et al., 2003).

Likelihood-ratio tests (LRTs) were used to determine the statistical significance of group differences on individual parameters, as well as of certain parameter estimates within a model. To conduct an LRT, a model in which the parameter(s) of interest is freely estimated is compared to a nested model in which this parameter is fixed (e.g., to 0 or equal across groups). The difference in χ^2 (i.e., the likelihood ratio) between the two models indicates the difference in fit, and if this difference is significant, the null hypothesis that the models fit equally well can be rejected (Kline, 2016). Given previous studies on the effects of aging and exercise on brain volume and structural integrity (Colcombe et al., 2006; Erickson et al., 2011; Köhncke et al., 2021), we had strong hypotheses that exercise would be beneficial to structural integrity of the brain. That is, those participants who exercised should show gains in or maintenance of structural integrity, while those who did not exercise would show declines in integrity. Therefore, unless otherwise indicated, one-sided hypothesis testing was conducted looking for changes in the positive direction within the EG and in the negative direction within the ACG.

Latent change score models (LCSMs) were used to evaluate group mean differences in change in VO_2peak and GM integrity following the tutorial by Kievit et al. (2018). Full details of the model validation can be found in the **Supplementary Material**, but we describe the models briefly in the following. A univariate LCSM was built to measure mean change in VO_2peak; a pseudo-latent factor, ΔVO_2peak, captured the difference in VO_2peak between T1 and T3. Multigroup models were used to test for differences in change between the two groups in cardiovascular fitness. Multivariate LCSMs with three time points were built to measure mean change in GM structural integrity from T1 to T2 as well as from T2 to T3 in each ROI individually. As is common practice in SEM, factorial invariance testing was performed to establish whether the measurement structure of the structural integrity models held across groups and time points. In those regions that survived invariance testing, mean differences in change between the two groups were investigated. Finally, in those models showing detectable individual differences in change as well as significant mean differences in change between groups, change-change correlations between fitness and GM structural integrity were examined using bivariate LCSMs (see **Figure 1**) both in the whole sample as well as separately for the two groups. This strategy was chosen to add credibility to a causal interpretation of change-change associations in the exercise group (see Ghisletta and Lindenberger, 2004). For an overview of the analysis plan of GM structural integrity models, see **Figure 2**.

RESULTS

A description of the sample can be found in **Table 1**. Participants who did not meet compliance criteria were excluded from T2 and T3 ($n_{ACG} = 3$, $n_{EG} = 10$) but were kept in at T1 under the assumption that they did not differ from other participants at baseline. One further exercise participant was excluded from T2 and T3 due to technical difficulties.

Cardiovascular Fitness

A univariate LCSM with one pseudo-latent difference score is exactly identified, therefore fit indices are perfect by definition. Cardiovascular fitness as indexed by VO_2peak showed a significantly positive mean change in the EG, unstandardized estimate of the mean (b_0) = 0.419 (i.e., average in increase of 0.419 mL/kg/min from T1 to T3), standard error (SE) = 0.089, $\Delta\chi^2_{(df\ =\ 1)} = 18.67$, $p < 0.001$, whereas mean change in the ACG was not significant, $b_0 = 0.123$, SE = 0.088, $\Delta\chi^2_{(df\ =\ 1)} = 1.92$, $p > 0.050$. Furthermore, the EG showed significantly greater mean change than the ACG, $\Delta\chi^2_{(df\ =\ 1)} = 5.37$, $p = 0.010$ (see **Figures 3**, **4**). In terms of percent change, the EG showed a mean change of 12.8% (SE = 2.28), while the ACG showed a mean change of 3.7% (SE = 2.22). A significant difference in VO_2peak between males and females was seen at baseline, $t(70.3) = 3.95$, $p < 0.001$, with males showing higher VO_2peak (mean = 25.5, SD = 5.99) than females ($M = 20.7$, SD = 4.46). Males and females did not differ in percent change in VO_2peak, and no associations of age or years of education were seen with either baseline or percent change in VO_2peak.

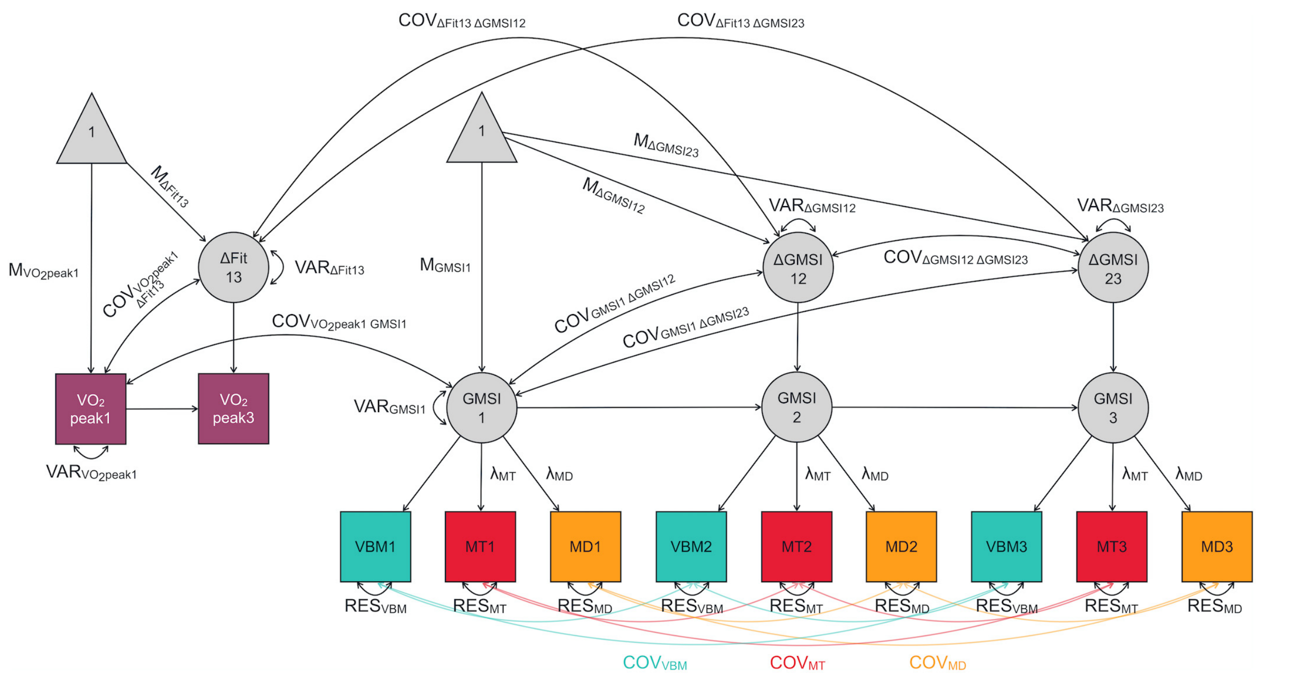

FIGURE 1 | Exemplary bivariate latent change score model measuring the covariance between change in cardiovascular fitness from T1 to T3 and change in gray-matter structural integrity in a given region of interest from T1 to T2 and T2 to T3. Fit, cardiovascular fitness; GMSI, gray-matter structural integrity; VBM, voxel-based morphometry-derived gray-matter probability; MD, mean diffusivity; MT, magnetization transfer saturation; 1, time point 1 (T1; 0 months); 2, time point 2 (T2; 3 months); 3, time point 3 (T3; 6 months); Δ, change; M, mean; COV, covariance; VAR, variance; λ, loading; RES, residual. Covariances between manifest variables of integrity were set to be equal within each modality, denoted by color-coding; these are only labeled once for visual clarity. Other unlabeled paths are fixed to 1.

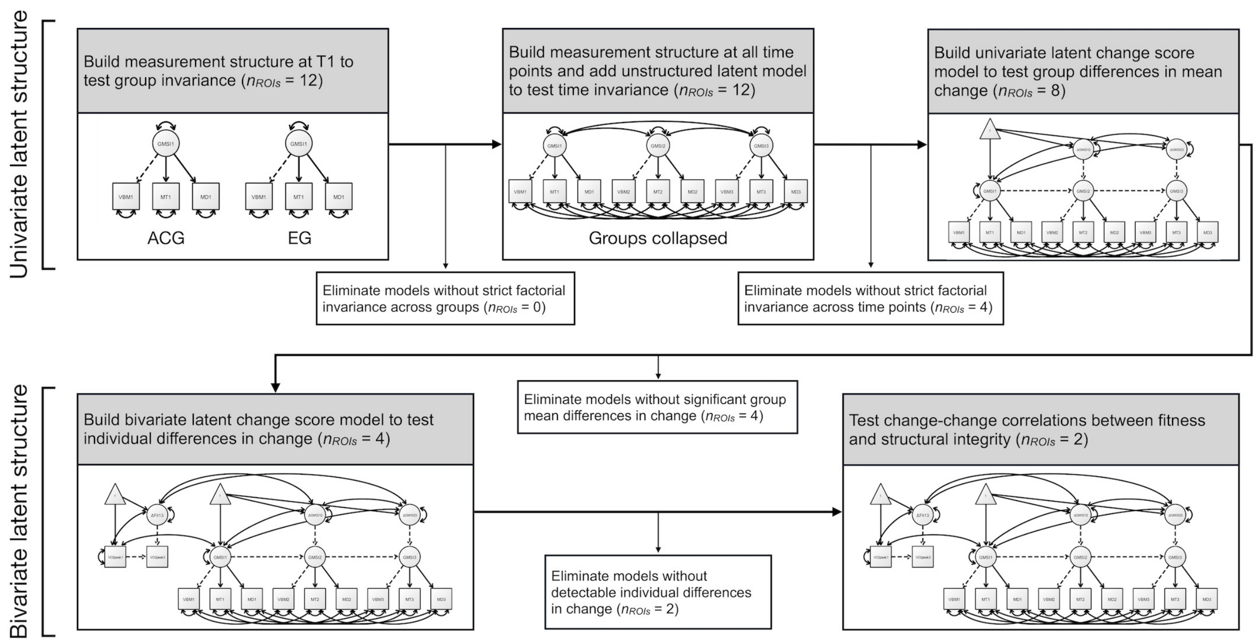

FIGURE 2 | Flowchart of the analysis plan of gray-matter structural integrity models including factorial invariance testing across groups and time points, testing for group mean differences in change, testing for significant individual differences in change, and testing for change-change correlations with fitness. T1, time point 1 (0 months). Model paths intentionally unlabeled for visual clarity. Dashed lines represent paths fixed to 1. See **Figure 1** for further model details.

TABLE 1 | Sample demographics and intervention specifics.

	Active control group	Exercise group
n completed intervention	35	40
n fully complied	32	29
Age at baseline, M/SD (range)	70.7/3.81 (64.0–76.0)	69.8/3.49 (63.9–76.9)
Sex, % of female participants	40.0	50.0
Years of education, M/SD (range)	13.4/3.27 (7–16)	13.2/3.02 (7–16)
DSST score at baseline, M/SD (range)	47.3/9.42 (31–68)	45.2/10.90 (21–75)
Total minutes spent in intervention, M/SD (range)	4772/1819.6 (2505–10,858)	6554/1222.9 (4098–9790)
Minutes spent reading, M/SD (range)	4772/1819.6 (2505–10,858)	3381/1143.3 (915–5855)
Minutes spent exercising, M/SD (range)	–	3173/410.4 (2556–3937)

M, mean; SD, standard deviation; DSST, Digit Symbol Substitution Test. Ms and SDs of age at baseline, sex, years of education, and DSST score at baseline are calculated within participants who completed the intervention. Total minutes spent in intervention are calculated within participants who fully complied to the intervention.

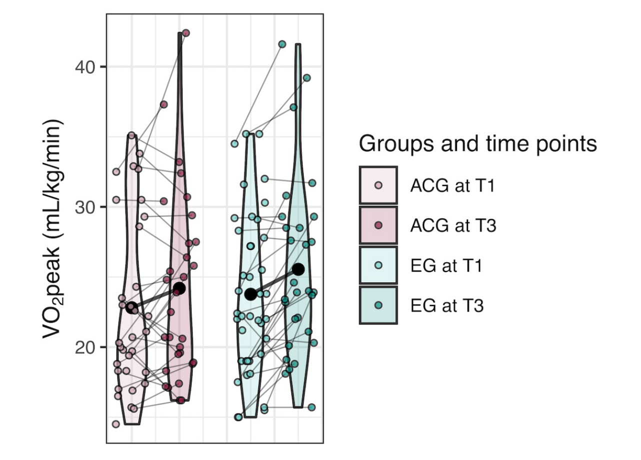

FIGURE 3 | Violin plots of VO_2peak showing individual trajectories as well as mean change of cardiovascular fitness change over six months by group. T1, time point 1 (0 months); T3, time point 3 (6 months). Large black point represents group mean at each time point.

Gray-Matter Structural Integrity

Out of the 12 initial GM structural integrity models, eight survived testing for factorial invariance, which implies that the factor structure did not vary across groups or time points: right and left hippocampus, right and left ACC, right PCC, right and left JLC, and right IFG. For these models, all standardized factor loadings were significant (*p*s < 0.050). In general, the variable with the highest loading was MD (average standardized loading = −0.857), revealing that this measure was the strongest indicator of latent GM structural integrity; next was VBM (0.527), followed by MT (0.463). See full model set-up results in **Table 2** for more details. Results for combined left and right hemispheres can be found in **Supplementary Material**.

Group Differences in Change

Group differences in mean change in structural integrity from T1 to T2 and from T2 to T3 were tested in those models that showed factorial invariance across groups and time points. All univariate LCSMs had acceptable fit indices, RMSEAs < 0.062 (95% CIs = [0, <0.116]), CFIs > 0.988. The EG showed significantly more positive change than the ACG in the right ACC from T1 to T2, in the left ACC from T2 to T3, in the right PCC from T2 to T3, and in the left JLC from T1 to T2 and from T2 to T3 (see **Table 2** and **Figure 4** for details). These group differences were primarily driven by mean decreases in GM integrity within the ACG: right ACC from T1 to T2, $b_0 = -0.042$, SE = 0.022, $\Delta\chi^2{}_{(df\ =\ 1)} = 3.68$, $p = 0.027$, left ACC from T2 to T3, $b_0 = -0.090$, SE = 0.027, $\Delta\chi^2{}_{(df\ =\ 1)} = 6.44$, $p = 0.006$, right PCC from T2 to T3, $b_0 = -0.064$, SE = 0.024, $\Delta\chi^2{}_{(df\ =\ 1)} = 9.05$, $p = 0.001$, left JLC from T2 to T3, $b_0 = -0.061$, SE = 0.028, $\Delta\chi^2{}_{(df\ =\ 1)} = 8.73$, $p = 0.002$. GM structural integrity did not significantly decline in the left JLC within the ACG from T1 to T2, nor did it significantly increase within the EG in any of the ROIs showing significant differences in group mean change. These time-by-group interaction effects were also detected when including age, sex, and years of education as indicator variables in the models, estimating means and residual variances of each, as well as regressions from each to baseline GM structural integrity, change from T1 to T2 and change from T2 to T3. In the following, we therefore discuss the simpler models, excluding these demographic factors, for the sake of parsimony.

Correlations Between Change in Cardiovascular Fitness and Change in Gray-Matter Structural Integrity

Two models, the right ACC and the left JLC, showed group differences in mean changes and reliable variance in change, thereby allowing us to investigate whether individual differences in fitness changes and individual differences in integrity changes were correlated. Both models had acceptable fit indices, RMSEAs < 0.059 (95% CIs = [0, <0.106]), CFIs > 0.987. Change in cardiovascular fitness was positively correlated with change in GM structural integrity in the right ACC from T1 to T2, standardized estimate (ϕ) = 0.753, $\Delta\chi^2{}_{(df\ =\ 1)} = 11.60$, $p < 0.001$, and in the left JLC from T1 to T2, $\phi = 0.469$, $\Delta\chi^2{}_{(df\ =\ 1)} = 6.42$, $p = 0.006$. Crucially, we observed a group difference in change-change correlation in the right ACC from T1 to T2, $\Delta\chi^2{}_{(df\ =\ 1)} = 4.52$, $p = 0.017$, with the ACG showing no significant correlation, $\phi = 0.424$, $\Delta\chi^2{}_{(df\ =\ 1)} = 1.92$, $p > 0.050$, and the EG showing a significantly positive correlation, $\phi = 1.110$, $\Delta\chi^2{}_{(df\ =\ 1)} = 10.54$, $p = 0.001$. These correlations were also detected when including age, sex, and years of education as indicator variables in the models, thus we discuss the results from the simpler models in the following.

DISCUSSION

This study used a multivariate, multigroup approach in SEM to investigate the effects of six months of at-home aerobic exercise

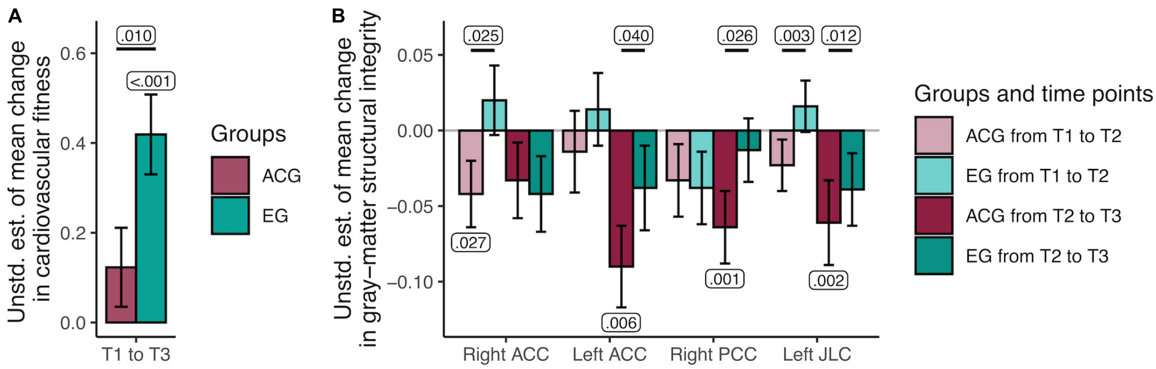

FIGURE 4 | Unstandardized parameter estimates of mean changes in cardiovascular fitness and gray-matter structural integrity by group. **(A)** Results of the univariate latent change score model (LCSM) of VO_2peak indicated that the active control group showed no mean changes in fitness, whereas the exercise group showed a significant mean increase in fitness over time. **(B)** Results of the multivariate LCSM of gray-matter structural integrity indicated that the active control group showed significant mean decreases in latent gray-matter structural integrity over time in the left and right anterior cingulate cortex, right posterior cingulate cortex, and left juxtapositional lobule cortex (previously supplementary motor area), while the exercise group exhibited maintenance in integrity in these regions. Unstd. est., unstandardized estimate; T1, time point 1 (0 months); T2, time point 2 (3 months); T3, time point 3 (6 months); ACG, active control group; EG, exercise group. Significant *p*-values of one-sided *t*-tests of individual parameters against zero (negative in ACG and positive in EG) as well as differences in group mean change are displayed. Error bars represent estimated SEs.

on cardiovascular fitness and a latent measure of GM structural integrity comprising multiple MR imaging modalities, which may be a more reliable measure of structural integrity than individual MR measures, such as GM volume. Change-change relationships between fitness and GM structural integrity were also explored.

Cardiovascular Fitness

Participants who engaged in interval training on a stationary bike at home for three to four days a week showed an increase in cardiovascular fitness, indexed by VO_2peak, over six months, and also improved more than an ACG who did not engage in regular aerobic exercise. This serves as a proof of concept for the current study, showing that the exercise intervention utilized in this sample was effective at improving cardiovascular fitness. Notably, the current design differs from previous exercise interventions that looked at exercise-induced changes in the brain in at least two dimensions: firstly, participants exercised at their own convenience in their homes, only coming to the lab once a week for a group stretching and toning session. This corroborates previous studies showing that regular at-home aerobic exercise can also improve cardiovascular fitness in older adults (King, 1991; Salvetti et al., 2008). This finding is important as regular exercise at home with only one supervised stretching and toning per week may be more accessible for an older population than personal training in a facility multiple times a week.

In addition to training taking place in participants' homes, the exercise regimes were also highly personalized and flexible. Initial difficulty for each participant was individually determined by a sports medicine physician, and during the intervention, participants could indicate the subjective perception of difficulty (i.e., too easy, too difficult) so that subsequent training could be modified accordingly. Participants were also not supervised during the exercise bouts. Still, this adaptive, at-home interval training regime was effective at increasing the cardiovascular fitness of those in the EG over those in the ACG. This is also in line with research on fitness improvements in aging; for example, one study found that older adults who adhered to a six-month exercise program at home under no supervision had greater VO_2peak at post-test than those who did not adhere, while the groups did not differ at baseline (Morey et al., 2003). Taken together, an adaptive, at-home aerobic exercise regime seems to be an effective intervention for improving cardiovascular fitness in healthy, previously sedentary older adults.

Gray-Matter Structural Integrity

The statistical analyses used in this study build on previous work (Kühn et al., 2017; Köhncke et al., 2021) in which a multimodal latent factor measuring GM structural integrity was established in a cross-sectional sample, and expanded this model for use in a longitudinal intervention study including three measurement time points to investigate patterns of change. Our results indicate that exercise promotes the maintenance (i.e., attenuated decrease) of structural integrity in regions of the brain that previously have been found to increase in volume in the course of an exercise intervention (Colcombe et al., 2006), namely the right and left ACC, the right PCC, and the left JLC (also termed supplementary motor area). These areas have been shown to undergo substantial age-related atrophy (e.g., Raz et al., 2005; Fjell et al., 2009), with exaggerated posterior atrophy found in patients with Alzheimer's disease (Lehmann et al., 2011). However, the vulnerability of brain structure to age-related effects in these regions seems to be accompanied by increased amenability to exercise- and physical fitness-induced maintenance and/or gains in older age (see also Colcombe et al., 2006; Ruscheweyh et al., 2011). It has been suggested before that intra-cortical myelin content may be one potentially important mechanism here (Walhovd et al., 2016), with high-myelin regions being more resistant to change, and regions with lower myelin content, such as the medial temporal

TABLE 2 | Testing for invariance across groups and time points, and testing for equal vs. unequal mean change parameters across groups.

Region of interest	Group invariance (T1)		Time invariance (groups collapsed)		Standardized estimates of factor loadings			Group difference in mean change	
	$\Delta\chi^2_{df=2}$ baseline vs. metric	$\Delta\chi^2_{df=3}$ metric vs. strict	$\Delta\chi^2_{df=4}$ baseline vs. metric	$\Delta\chi^2_{df=6}$ metric vs. strict	VBM	MT	MD	$\Delta\chi^2_{df=1}$ ΔSI T1 to T2	$\Delta\chi^2_{df=1}$ ΔSI T2 to T3
Right HC*	0.33	4.34	0.69	4.67	0.792†	0.576†	−0.887†	0.48	0.09
Left HC*	0.51	4.19	2.18	4.51	0.751†	0.464†	−0.987†	1.33	0.42
Right ACC*	2.82	2.49	6.08	2.53	0.596†	0.518†	−0.895†	3.87†	0.38
Left ACC*	1.78	1.20	5.60	8.06	0.278†	0.632†	−0.256†	1.85	3.07†
Right PCC*	4.01	0.69	0.00	4.49	0.494†	0.418†	−1.000†	0.75	3.75†
Left PCC	0.00	6.21	17.12†	–	–	–	–	–	–
Right PCG	0.00	1.28	10.16†	–	–	–	–	–	–
Left PCG	4.64	2.33	10.85†	–	–	–	–	–	–
Right JLC*	1.57	3.29	1.07	12.19	0.412†	0.417†	−0.942†	0.95	1.87
Left JLC*	1.15	0.90	2.82	7.49	0.478†	0.415†	−0.931†	7.45†	5.05†
Right IFG*	0.44	5.37	0.00	9.77	0.416†	0.263†	−0.957†	2.34	0.15
Left IFG	5.02	1.44	19.10†	–	–	–	–	–	–

HC, hippocampus; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; PCG, precentral gyrus; JLC, juxtapositional lobule cortex; IFG, inferior frontal gyrus; ΔSI, change in structural integrity.
**Model shows factorial invariance across groups and time points.*
†$p < 0.050$. Factorial invariance can be assumed if the measurement invariance test is non-significant (two-sided), meaning the model fit does not significantly worsen if parameters are set to be equal across groups/time points. Significance of standardized factor loadings tested using a Wald test (one-sided). A group difference in mean change can be inferred if the p-value is significant (one-sided), meaning the model fit significantly worsens when the parameter is constrained to be equal across groups.

lobe and cingulate cortices (Grydeland et al., 2013), being more prone to change in both the negative and positive direction.

The latent factor of GM structural integrity as established in this study captured the variance common to VBM, MT, and MD. Köhncke et al. (2021) reported that older individuals showed lower factor scores in the prefrontal cortex, hippocampus, and parahippocampal gyrus. This suggests that lower factor scores may be indicative of greater GM deterioration that occurs during normal aging, which could be caused by various and potentially correlated structural changes, including loss of dendritic spines and dendritic arbors, decreasing synaptic density, demyelination, and loss of glia and small blood vessels (Hof and Morrison, 2004; Morrison and Baxter, 2012; Zatorre et al., 2012; Raz and Daugherty, 2018). Considering the single indicators, the factor loadings indicate that lower factor scores result from a pattern of lower VBM, lower MT, and higher MD values, which are thought to reflect lower estimates of GM volume, myelination, and density, respectively. Therefore, a factor score capturing the shared variance between these indicators seems to represent general properties of GM structure that decline with age. Further supporting their interpretation that the latent factor reflects structural integrity, Köhncke et al. (2021) were also able to show a positive association between the latent factor and a latent factor comprising four episodic memory tasks, which is in line with the brain maintenance hypothesis that brain integrity across multiple levels is important for cognitive performance (Nyberg et al., 2012; Lindenberger, 2014; Cabeza et al., 2018; Nyberg and Pudas, 2019; Nyberg and Lindenberger, 2020; Johansson et al., 2022).

Here, we established the same latent factor of GM structural integrity in a longitudinal design encompassing three time points. The assumption of factorial invariance across two groups and three time points was found to be tenable for the right and left hippocampus, right and left ACC, right PCC, left JLC, and right IFG. In the right and left ACC, right PCC, and left JLC, the ACG showed decreases in integrity, while the changes in the EG were significantly more positive, indicating that the exercise intervention had helped to maintain structural integrity in these areas. This supports the hypothesis that exercise has a neuroprotective effect on general structural integrity in older adults in areas of the brain where effects of exercise on volume have been observed before (e.g., Colcombe et al., 2006).

One mechanism hypothesized to underlie the relationship between aerobic exercise and brain structure is the increase in cerebral blood flow that occurs during bouts of exercise. In response to a complex combination of partial pressure of arterial carbon dioxide and oxygen, blood pressure, cerebral metabolism, and neurogenic regulation, acute physical exercise increases cerebral blood flow (Querido and Sheel, 2007; Smith and Ainslie, 2017), bringing with it oxygen and nutrients. With more resources available, both neurons and the surrounding cells may be better sustained, which would then be reflected in the latent factor of structural integrity. In contrast, individuals in the ACG, who did not engage in aerobic exercise, were less likely to experience this regular increase in cerebral blood flow, to the effect that GM structural integrity would be more likely to continue on a downward trajectory. Indeed, one study, a short-term exercise intervention (12 weeks) in older adults, even found an increase in cerebral blood flow at rest in the ACC within an exercise group vs. a control group (Chapman et al., 2013).

Notably, varying patterns of the timing of structural integrity changes were seen across ROIs. In the right ACC, the difference between groups in integrity change was seen in the first 3 months of the intervention, while in the left ACC and right PCC, this difference was seen in the second three months, and in the left

JLC, this difference was evident throughout the six months. To some degree, group differences in change may have emerged only later in the study because unspecific initial interventions effects may have been shared across both conditions. The active control participants, though not engaging in exercise training, also changed their daily and weekly routines to incorporate more interaction with technology (tablet use), as well as with new social partners (weekly group sessions), which might have constituted a departure from their usual routine with potentially beneficial effects, in line with work suggesting positive associations between brain maintenance, cognition, and an active lifestyle (Lövdén et al., 2005; Hertzog et al., 2008; Nyberg et al., 2012; Small et al., 2012; Mintzer et al., 2019). However, to the degree that they habituated to these new daily practices, the initial overall effect might have worn off, while the mechanisms conveying a positive effect of exercise on brain integrity continued to operate in EG participants. Conversely, participants in the EG may have experienced initial maintenance in structural integrity at the beginning of their new training regimes, but as their brain and vascular systems grew more accustomed to the impulse afforded by aerobic exercise, a normal trajectory of decline might have resumed. Given the small sample size, these considerations are clearly speculative. More research is needed to better understand the cascade of mechanisms that convey benefits of aerobic exercise on different areas of the aging human brain.

Positive Correlation Between Change in Cardiovascular Fitness and Structural Integrity in the Right Anterior Cingulate Cortex and Left Juxtapositional Lobule Cortex

Finally, in the right ACC and the left JLC, we were able to reliably measure significant individual differences in change, allowing us to investigate change-change correlations with cardiovascular fitness. A positive correlation was found between change in cardiovascular fitness and change in right ACC structural integrity from T1 to T2 in exercisers but not controls, indicating that those exercisers who gained more cardiovascular fitness during the intervention also showed less decline in structural integrity in the right ACC during the first 3 months of the intervention. A positive correlation was also found between change in cardiovascular fitness and change in left JLC structural integrity from T1 to T2, but this correlation did not differ between groups.

Many cross-sectional studies investigating the relationship between cardiovascular fitness and brain structure (using a single indicator approach) in older adults have found positive associations between fitness and in frontal areas, temporal areas, or both, as well as parietal, posterior (e.g., precuneus), and sub-cortical (e.g., caudate) areas (see review by d'Arbeloff, 2020). Similarly, some non-intervention longitudinal studies have reported positive associations between fitness and brain structure in similar brain regions (see d'Arbeloff, 2020), and one study found that baseline cardiovascular fitness was related to the progression of dementia severity and brain atrophy in Alzheimer's patients (Vidoni et al., 2012). The current findings extend this previous work by reporting a change in the right ACC that is likely to reflect a causal effect of a change in cardiovascular fitness.

The current study has a number of limitations that should be addressed in future studies. First, the sample size was relatively small, especially for SEM. This might help to explain why individual differences in change often failed to differ reliably from zero. The current sample is also relatively homogeneous; healthy, previously sedentary older adults from an area with relatively high socioeconomic status were recruited to participate and were further screened for health conditions before being allowed to participate in the study. Healthy sedentary adults might be equipped with a range of protective factors that keep them healthy in the presence of a lifestyle that might result in deteriorating health in most other individuals. Thus, the generalizability of the present results to other segments of the aging population is unclear.

CONCLUSION

In this study, we introduced a multimodal modeling approach for investigating the effects of aerobic fitness interventions on regional GM structural integrity in human aging. Our findings corroborate and extend earlier results by showing that at-home aerobic exercise among healthy sedentary older adults results in improved cardiovascular fitness and helps to maintain GM structural integrity in areas that have been found to show exercise-induced volume changes.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are publicly available. The data and relevant scripts for analysis can be found here: https://osf.io/yw865/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the German Psychological Society (DGPs). The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SP assisted with data acquisition, analyzed the data, interpreted the results, and wrote the manuscript. MK preprocessed imaging data and revised the manuscript. YK and AB assisted with SEM analysis and revised the manuscript. NB designed the neuroimaging protocol and revised the manuscript. CM and JP performed physical assessments including cardiopulmonary exercise testing and revised the manuscript. BW designed the physical assessment protocol and revised the manuscript. SK designed the study and revised the manuscript. UL and SD designed the study, interpreted the results, and revised the manuscript. EW designed the study, preprocessed imaging data, interpreted the results, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2022.852737/full#supplementary-material

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