PHYSICAL ACTIVITY: AN OPTIMIZER OF THE NEUROPHYSIOLOGICAL SYSTEM?

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PHYSICAL ACTIVITY: AN OPTIMIZER OF THE NEUROPHYSIOLOGICAL SYSTEM?

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EDITORIAL
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Editorial: Physical Activity: An Optimizer of the Neurophysiological System?

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Keywords: exercise, neurophysiology, nervous system, brain, executive functions, quality of life, aging, detraining

Editorial on the Research Topic

Physical Activity: An Optimizer of the Neurophysiological System?

From the field of neurophysiology, broadly defined as the study of the nervous system function, numerous researches have studied the central and peripheral nervous systems from whole organs to subcellular compartments.

Different studies focused on physical activity and health have shown the impact of performing a physical fitness test on the simultaneous performance of a cognitive task, or the effects of exergames on heart rate variability in women with fibromyalgia (Villafaina et al., 2018, 2020). Other studies focused on cognitive performance have shown the psychophysiological stress response of adolescent chess players during problem-solving tasks (Fuentes-Garcia et al., 2019) or the electroencephalographic response of chess players in decision-making processes under time pressure (Villafaina et al., 2019).

In the same sense, different studies have shown that physical exercise improves the efficiency of the capillary system and increases the supply of oxygen to the brain, affecting the improvement of metabolic activity and oxygen intake in neurons (Kaliman et al., 2011). This positively influence different brain functions (e.g., attention) (de Bruin et al., 2016), and aerobic physical exercise may improve brain neurophysiological activity during the resolution of a selective attention test (Ferro et al., 2019) or working memory performance (Hsieh et al., 2018).

Consequently, there is evidence that participation in physical activity may modify white matter integrity and activation of regions key to cognitive processes. However, additional larger hypothesis-driven studies are needed to replicate findings (Valkenborghs et al., 2019). Physical activity buffers the negative effects of stress on cognitive performance in children (Wunsch et al., 2019), and may have a positive effect on memory, executive functions, and on genes associated with neuroprotective anti-aging resilience signaling (Corpas et al., 2019).

The main objective of this Research Topic was to gather studies that shed more light on the benefits of physical exercise in the neurophysiological system, from childhood to old age and from the field of health to sports or professional performance. For example, we consider important those studies that deepen into the epigenetic mechanisms involved in the aging process and their modulation through physical exercise, improving prevention and treatment therapies, and those that contributes to better understand how physical

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activity improves brain functions (e.g., increased hippocampal), or what effect cognitive loads cause in variables such as heart rate variability or brain waves. We also consider it particularly interesting to show studies that can reflect how physical exercise can be a good preventive strategy to avoid or counteract neurodegenerative diseases, such as Alzheimer, and consequently, increase the time and quality of life.

Thus, some of the topics of interest for this Research Topic are studies that contemplate the latest advances on neurophysiological and epigenetic effects of physical exercise on the aging, or beneficial effects of the practice of physical activity and sport on anti-aging and neuroprotective mechanisms. Equally relevant aspects to consider are the effects of physical exercise to prevent neurodegenerative diseases, the relationship between physical exercise practice and improvement of brain functions, the effects of cognitive loads at the neurophysiological level, or the neurophysiological system behavior related to sports or professional performance.

The influence of physical fitness in the nervous system structure is examined by Best et al. in siblings to estimate the contribution of genetic and environmental factors to variation within physical fitness and brain structure. Although performance-based measures of fitness were not associated with any structural neuroimaging markers, greater body mass index is associated with lower white matter integrity.

The effects of stress and lifestyle factors have been assessed with biomarkers like telomere length and telomerase activity which may have the potential to help the understanding of the stress-aging relationship and potential underlying mechanisms in elite athletes (Mehrsafar et al.).

The benefits of exercise are documented for different diseases. Even though it is still to define the exercise intensity and frequency required to improve patients' autonomic modulation, positive effects provided by exercise programs enhanced by resistance and endurance are found in cancer patients and survivors as demonstrated by Lavín-Pérez et al..

The study performed by Chi-Fang Lin et al. suggests that in children with Attention-Deficit/Hyperactivity Disorder Theta/Beta Ratios may be one of the mechanisms between motor ability and inhibition function.

Still concerning pathological conditions, Villafaina et al. explained that the performance during motor–cognitive dual and single tasks in women with fibromyalgia show the same electrical brain activity pattern whereas healthy ones adapt brain activity to task commitment.

Among heroin addicts, Wang et al. demonstrated that aerobic exercise attenuates heroin cravings and promotes inhibitory control showing its efficacy when dealing with this condition.

Exercise has been shown to optimize older adults sleep, especially, when moderate-intensity continuous training and stretching are considered, showing greater efficacy than high-intensity interval training (Bullock et al.). A similar effect is found concerning stress in different age populations confirming the health-enhancing effect of acute exercise (Mücke et al.) and physical activity amount on some of the physiological and psychological stress reactivity indicators as well as the central fatigue and perceived exertion (de la Vega et al.).

The neuroprotective effect of exercise in the aging process has been explored by Burgos et al. Executive function in normally aging adults has shown to beneficiate from the practice of exercise. An additional gain is exhibited when to the physical exercise, mental training is added, probably through more efficient early attentional processing.

This book explores some of the most UpToDate issues and raises questions to be answered by further research. Hopefully, this collection will stimulate this issue study.

AUTHOR CONTRIBUTIONS

JF-G, RR-C, MG-C, and MC conceived and designed the Research Topic and wrote the editorial. All authors contributed to the article and approved the submitted version.

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Acute Aerobic Exercise Ameliorates Cravings and Inhibitory Control in Heroin Addicts: Evidence From Event-Related Potentials and Frequency Bands

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Objective: Aerobic exercise is considered a potential adjunctive treatment for heroin addicts, but little is known about its mechanisms. Less severe cravings and greater inhibitory control have been associated with reduced substance use. The aim of the current study was to determine the effects, as measured by behavioral and neuroelectric measurements, of acute aerobic exercise on heroin cravings and inhibitory control induced by heroin-related conditions among heroin addicts.

Design: The present study used a randomized controlled design.

Methods: Sixty male heroin addicts who met the DSM-V criteria were recruited from the Isolated Detoxification Center in China and randomly assigned to one of two groups; one group completed a 20-min bout of acute stationary cycle exercise with vigorous intensity (70–80% of maximum heart rate, exercise group), and the other group rested (control group). The self-reported heroin craving levels and inhibitory control outcomes (measured by a heroin-related Go/No-Go task) were assessed pre- and post-exercise.

Results: The heroin craving levels in the exercise group were significantly attenuated during, immediately following, and 40 min after vigorous exercise compared with before exercise; moreover, during exercise, a smaller craving was observed in the exercise group than in the control group. Acute exercise also facilitated inhibition performance in the No-Go task. After exercise, the participants' accuracy, the N2d amplitudes, and the theta two band spectral power during the No-Go conditions were higher in the exercise group than in the control group. Interestingly, significant correlations between the changes in these sensitive measurements and the changes in cravings were observed.

Conclusions: This is the first empirical study to demonstrate that aerobic exercise may be efficacious for reducing heroin cravings and promoting inhibitory control among heroin addicts.

Keywords: acute aerobic exercise, heroin addicts, inhibitory control, N2d, theta

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INTRODUCTION

Heroin addiction is becoming more common globally and is thus a major public health problem. The relapse rate of heroin addicts, which is considered a major persistent obstacle to rehabilitation treatment (Stewart, 2008), remains high after 1 year of treatment programs (Carroll et al., 1994), and new approaches to treatment are needed. Previous research suggests that aerobic exercise may be a useful adjunctive treatment for drug addicts (including heroin addicts), although the evidence is from exploratory research (Smith and Lynch, 2012; Pareja-Galeano et al., 2013). In creating an evidence base, it is important to establish plausible mechanisms. Previous studies suggest that more severe cravings for substances and lower levels of inhibitory control predict substance use; therefore, treatments that reduce cravings and promote inhibitory control may be useful (Volkow et al., 2016). The beneficial effects of aerobic exercise on cravings for other substances [e.g., methamphetamine (Wang et al., 2015), cigarettes (De La Garza et al., 2016; Abrantes et al., 2017), and alcohol (Hallgren et al., 2017)] have been widely reported. Only a few empirical studies have reported that heroin cravings become less severe after acute aerobic exercise (Bailey et al., 2011). Therefore, it is important to understand the effects of aerobic exercise on heroin addiction and related psychological mechanisms.

Although multiple factors contribute to the probability of a craving, evidence suggests that executive function impairment contributes to heroin use and relapse from treatment (Morie et al., 2014; Stevens et al., 2014). Chronic heroin abuse is associated with executive dysfunction, particularly inhibitory control dysfunction (Stevens et al., 2014; Volkow et al., 2016). Inhibitory control impairment makes it difficult for individuals to resist the temptation of drug cues and impulsive thoughts and behaviors of intake. Moreover, neuroimaging studies have further demonstrated that, relative to healthy groups, heroin addict groups exhibit abnormal structures and lower levels of activation in brain regions related to inhibitory control during the Go/No-Go task, including impairments in the bilateral medial prefrontal gyrus, bilateral anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DPFC), left middle frontal gyrus (MFG), and left insular and bilateral inferior frontal gyrus (IFG) (Fu et al., 2008; Luijten et al., 2014; Moningka et al., 2018). Inhibitory control failure and associated brain dysfunction are key underlying factors of relapse and addiction (Su et al., 2017). Therefore, inhibitory control may be an important factor related to aerobic exercise in reducing the risk of relapse in heroin addicts.

A substantial body of systematic studies on acute aerobic exercise and executive function interactions have shown that acute aerobic exercise can positively modulate inhibitory control (Chang et al., 2012; Basso and Suzuki, 2017; Li et al., 2017). Moreover, many empirical studies have also shown that acute aerobic exercise has a positive effect on inhibitory control in various paradigms, including the Go/No-Go task (Kamijo et al., 2004), stop-signal task (Chu et al., 2015), and flanker task (Hillman et al., 2006). This beneficial effect of acute exercise has also been observed in other groups of individuals with brain dysfunction, such as those with attention-deficit hyperactivity disorder (Gapin et al., 2015; Mehren et al., 2019), Alzheimer's and Parkinson's disease (Paillard et al., 2015), and aging (Barnes, 2015). In addition, neuroimaging studies have revealed significant levels of activation in some brain regions associated with inhibitory control after acute aerobic exercise, including the ACC, IFG, and vermis cerebelli (Krafft et al., 2013; Fontes et al., 2015). More importantly, acute aerobic exercise facilitates inhibitory control in individuals with methamphetamine addiction (Wang et al., 2015), and this previous study demonstrated improved inhibitory control after acute aerobic exercise, providing preliminary evidence that acute aerobic exercise is beneficial for individuals with drug addictions. From the above results, functional complementarity and majority overlapping in the cortical structure may exist, indicating that it is highly likely that acute aerobic exercise can modulate inhibitory control in heroin addicts.

The vast majority of electroencephalogram (EEG) studies have characterized inhibitory control dysfunction in heroin addicts using event-related potentials (ERPs) associated with the Go/No-Go task (Morie et al., 2014; Steele et al., 2014; Yang et al., 2015; Su et al., 2017). These studies have shown that the N2 component is sensitive in measuring the dysfunction of heroin addicts under No-Go conditions. The largest negative-going peak over the fronto-central cortex occurs within 200–300 ms of stimulus onset in the N2 component. The N2 can reflect features of conflict monitoring; features of cognitive control processing (Falkenstein, 2006; Folstein and Van Petten, 2008; Groom and Cragg, 2015), which is a top-down cognitive mechanism in the early stages of inhibitory control; and a reduction in the N2 amplitude during the No-Go task, which is a sensitive indicator of impaired inhibition in heroin addicts (Morie et al., 2014; Su et al., 2017). Moreover, to more clearly highlight the effects on inhibitory control processing that were mentioned above, N2d, which is defined as the difference in signals from the No-Go trials and those from the Go trials, is widely used (Cao et al., 2017; Su et al., 2017). In addition to the ERP components mentioned above that are related to inhibitory control, the changes in spectral power that occur with performance in the Go/No-Go task have also been studied by many researchers. The changes in the spectral power of EEG signals reflect the processing of neuron rhythm adjustments induced by a stimulus, such as an excitatory or inhibitory stimulus, and the spectral power in different frequency bands are often related to various cognitive activities performed by human beings (Klimesch et al., 2007; Nguyen et al., 2017). Moreover, the theta (4–8 Hz) bands are strongly affected by the Go/No-Go paradigm (Cavanagh and Frank, 2014; Nguyen et al., 2017). The spectral power of the event-related theta band (4–8 Hz) is related to fronto-limbic interactions (Karakaş et al., 2000) and is associated with high-order cognitive processes involved in top-down control (Cavanagh et al., 2012; Cavanagh and Frank, 2014) and response conflict (Cohen and Cavanagh, 2011). Previous studies have suggested that lower levels of theta-band power are associated with poorer inhibitory functions (Motlagh et al., 2017; Fielenbach et al., 2019).

In the current study, we used a randomized controlled design to test the effects of acute aerobic exercise on cravings and inhibitory control among heroin addicts. The intensity of aerobic exercise used was vigorous intensity (70–80% of maximum heart rate), which is the most suitable model for heroin addicts (Bailey et al., 2011; Colledge et al., 2017). Additionally, we evaluated inhibitory control in heroin addicts from behavioral and neuroelectric perspectives (e.g., ERPs and spectral power) with the Go/No-Go task, which is related to heroin cues. We hypothesized that acute aerobic exercise with vigorous intensity would decrease heroin cravings, improve behavioral performance, and facilitate neuroelectric activation-related inhibitory control.

MATERIALS AND METHODS

Participants

Sixty male heroin addicts aged between 20 and 40 years were recruited from the Yunnan Compulsory Isolated Detoxification Center in China. All participants met the criteria for Diagnosis and Statistics of Mental Disorder 5th edition (DSM-V) for heroin addicts. The inclusion criteria included (a) intact color vision, (b) a normal level of intelligence, (c) the absence of a history of neurological diseases or physical disabilities, and (d) the absence of medical contraindications for high-intensity exercise, as determined by the Physical Activity Readiness Questionnaire (PAR-Q) (American College of Sports Medicine, 2013). The participants were randomly assigned to either the aerobic exercise or sedentary control group. The demographic characteristics of the two groups are summarized in **Table 1**. Before participating in the study, all participants signed a consent form, which was approved by the Ethics Committee of Ningbo University.

Measurements

Cravings

The self-reported craving level measured the strength of heroin desire using a visual analogue scale (VAS) (Sayette et al., 2000). The VAS rated on a scale from 0 = "no craving at all" to 10 = "extremely craving". After watching a series of randomly presented heroin-related images including forms of heroin, heroin paraphernalia, and heroin-related scenes on iPad, the participant was required to mark on a 10-cm line.

Inhibitory Control

For the Go/No-Go task, heroin cue images and neutral cue images with either blue or yellow frames were presented at a visual angle of 10.3° × 14.8° via E-prime software (E-prime 2.0, Psychology Software Tools, Inc., United States), as described in our previous work, to assess the inhibitory control (Wang et al., 2015). Fifteen neural images (valence: 5.23; arousal: 5.33) were selected from the Chinese Affective Picture System (Lu et al., 2005). The fifteen heroin-related images (valence: 4.12; arousal: 4.37) depicted various forms of heroin, heroin paraphernalia, and heroin-related scenes, which were selected based on the results of a nine-point self-rating scale from another 36 heroin addicts. The heroin-related and neutral images were carefully selected so that they matched in terms of luminance, contrast, and spatial frequency. Each image with a frame was rapidly

TABLE 1 | Participants' demographic characteristic (mean ± SD/n+%).

	Exercise (n = 30)	Control (n = 30)	t/χ^2
Demographic			
Age (years)	32.73 ± 7.15	32.40 ± 7.76	0.86
Height (cm)	170.48 ± 7.03	168.44 ± 5.62	0.23
Weight (kg)	61.88 ± 8.81	62.42 ± 9.11	0.42
IQ (PR)	10.50 ± 10.03	10.50 ± 8.34	1.00
SES			
Marriage			
Single	10 (33.33%)	10 (29.4%)	0.84
Married	11 (36.67%)	12 (35.3%)	
Live together	1 (3.33%)	4 (11.8%)	
Divorce	6 (20.00%)	7 (20.6%)	
Widowed	2 (6.67%)	1 (2.9%)	
Education			
Elementary	16 (53.33%)	13 (43.33%)	0.67
Junior	13 (43.33%)	15 (50.00%)	
Senior	1 (3.33%)	2 (6.67%)	
Occupation			
Farm laborer	16 (53.33%)	13 (43.33%)	0.22
Self-employed	3 (10.00%)	10 (33.33%)	
Manual worker	2 (6.67%)	1 (3.33%)	
General staff	1 (3.33%)	2 (6.67%)	
Civil servants	1 (3.33%)	0 (0%)	
Peasant laborer	4 (13.33%)	3 (3.33%)	
Not employed	3 (10%)	1 (3.33%)	
Family income (100 yuan/month)	38.13 ± 31.84	28.88 ± 28.65	0.24
Smoke data			
Usage (n)	30 (100%)	30 (100%)	1.00
Duration (years)	16.46 ± 6.73	17.68 ± 7.72	0.48
Frequency (cigarette/day)	20.27 ± 13.10	21.93 ± 13.82	0.63
Alcohol data			
Usage (n)	18 (60%)	18 (60%)	1.00
Duration (year)	11.60 ± 8.24	11.64 ± 9.84	0.98
Frequency (time/week)	2.80 ± 4.05	2.10 ± 3.19	0.46
Heroin data			
Usage (g/time)	0.35 ± 0.40	0.35 ± 0.31	0.97
Frequency (time/month)	66.60 ± 42.19	79.07 ± 61.45	0.37
Duration (year)	7.00 ± 6.07	7.83 ± 5.68	0.59
Relapse (time)	3.27 ± 3.56	3.93 ± 9.11	0.71
Fitness and physical activity			
DBP (mmHg)	73.26 ± 9.10	69.05 ± 13.27	0.12
SBP (mmHg)	127.69 ± 15.11	125.65 ± 14.21	0.52
Resting HR (bpm)	76.12 ± 11.36	75.24 ± 11.32	0.43
VO_{2max} (ml/kg/min)	2.47 ± 1.17	2.59 ± 1.00	0.71
BMI (kg/m^2)	21.29 ± 1.74	22.01 ± 3.17	0.56
IPAQ (1000 MET/week)	20.68 ± 16.81	19.37 ± 17.59	0.78
Emotional status			
SAS	53.43 ± 9.95	52.13 ± 8.78	0.61
SDS	50.53 ± 14.80	47.70 ± 12.31	0.42

SES, socioeconomic status; resting HR, resting heart rate; DBP, diastolic blood pressure; SBP, systolic blood pressure; IQ, reven's standard test of intelligence (percentile rank, PR); IPAQ, international physical activity questionnaire (100 MET/week); SAS, self-rating anxiety scale; SDS, self-rating depression scale. VO_{2max} was evaluated using an Astrand-Rhyming cycle ergometer-based cardiorespiratory fitness test (evaluated based on VO_{2max}).

presented one by one on a gray background with a presentation time of 300 ms and an interstimulus interval that randomly varied from 600 to 900 ms (see **Figure 1**). The participants were instructed to respond to images with a yellow frame (i.e., Go trial: Go-Neutral or Go-Heroin) as quickly as possible by pressing the space bar but to withhold their response when an image had a blue frame (i.e., No-Go trial: No-Go-Neutral or No-Go-Heroin). Three blocks were administered, consisting of 150 Go trials and 50 No-Go trials with equal probability of occurring in a quasi-random order.

Procedure

Several types of background information were gathered during the baseline tests, including the participants' demographic characteristics, socioeconomic statuses, medical histories, smoking habits, alcohol consumption habits, heroin dependence, and physical activity; their emotional statuses were assessed via the Self-rating Depression Scale (SDS) and the Self-rating Anxiety Scale (SAS). The eligible participants then underwent the Astrand-Rhyming fitness test, and their body mass index (BMI) values were recorded.

The heroin addicts were randomly assigned to the exercise group or control group with the aid of a computer algorithm[1] after baseline testing. The participants in the exercise group were engaged in a vigorous-intensity aerobic exercise program that involved a 5-min warm-up, a 20-min main exercise period, and a 5-min cool down. During the main exercise period, the participants were instructed to complete a bout of stationary cycle exercise and adjust the load so that their the heart rate (HR) remained within 70–80% of their maximum HR (HR max = 206.9–0.67 × age). HR was monitored using PolarRCX3 (Polar Company, Finland). The participants' HR and rating of perceived exertion (RPE) were recorded every 2 min throughout the exercise period. The mean HR for this exercise was 146.36 ± 4.39 bpm, which equated to 78.61 ± 1.57% of the maximum HR. Additionally, the mean RPE score was 14.93 ± 1.08. Participants in the control group were required to read about heroin treatments in a quiet room for 30 min.

The VAS score was measured at several time points, including before the cognitive pre-test, before the warm-up, during the exercise period, immediately after the exercise period, and after the cognitive post-test. In addition, before the warm-up and after the exercise period, when their HR returned to within 110% of their resting HR levels, the participants were required to complete the heroin-related Go/No-Go task with an EEG cap. The total duration of the experimental procedure was approximately 100 min.

[1]http://www.random.org

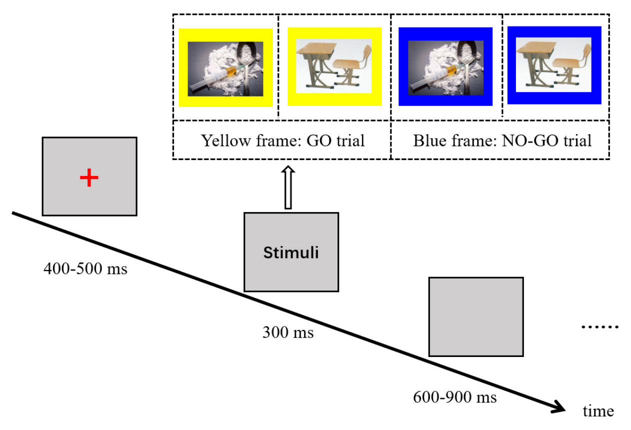

FIGURE 1 | Illustration of the heroin-related Go/No-Go task. Press the space bar as quickly as possible when the stimulus interface presents an image with a yellow frame (i.e., Go trial: Go-Neutral or Go-Heroin) but withhold the response when an image with a blue frame is presented (i.e., No-Go trial: No-Go-Neutral or No-Go-Heroin).

Electroencephalographic Recording and Data Processing

The EEG signals were recorded using a 32-channel Ag/AgCl electrode cap (10–20 International System), a Brain Amp amplifier, and a Brain Vision Recorder 2.0 system (Brain Products Company, Germany). The EEG signals were referenced to FCz and grounded to the AFz electrode. Horizontal and vertical electrooculography (HEOG and VEOG) signals were recorded from the outer canthi of the right eye and the infraorbital region of the left eye, respectively. In addition, the EEG signals were amplified using a bandpass filter from 0.01 to 100 Hz and sampled at a rate of 1000 Hz. The impedance of each electrode remained below 5 kΩ.

We used the Brain Vision Analyzer 2.0 system (Brain Products Company, Germany) to analyze the EEG data offline. After the EEG signals were re-referenced to the average signal from the bi-mastoid electrodes, they were bandpass filtered from 0.5 to 100 Hz, and EOG artifacts were corrected by the independent component analysis (ICA) algorithm. Trials with artifacts that exceeded ± 100 μv were rejected. The EEG was segmented into the epoch using stimulus locked from −200 to 800 ms for correct trials, and baseline correction was performed using the 200-ms pre-stimulus period. The N2 and difference in N2 waves (i.e., N2d) were measured. In addition, the EEG signals were analyzed by fast Fourier transform before overlay averaging, and then, the spectrum power of the frequency bands for theta 1 (4–6 Hz) and theta 2 (6–8 Hz) was obtained.

Statistical Analysis

Independent t-test and Chi-square test were employed to analyze differences in demographic characteristics between the exercise and control groups. Regarding cravings, 2 (group: exercise and control) × 5 (time point: pre-test, pre-exercise, during exercise, post-exercise, and follow-up) repeated-measures analysis of variance (RM-ANOVA) was performed. Regarding the behavioral data (including Go-RT, Go accuracy, and No-Go accuracy) for the heroin-related Go/No-Go task, 2 (group) × 2 (time point: pre-test and post-test) × 2 (condition: heroin cue and neutral cue) RM-ANOVA was performed. Regarding the N2 data and spectrum power data, 2 (group) × 2 (time point) × 4 (condition: heroin Go, neutral Go, heroin No-Go, and neutral No-Go) × 4 (site: Fz, FCz, Cz, and Pz) RM-ANOVA was performed, and the 2 (group) × 2 (time point) × 4 (site) RM-ANOVA was performed to analyze the N2d data from the two conditions. Additionally, the correlations between the changes in the main outcomes, defined as the differences between the post-test and pre-test (represented by the symbol Δ), were analyzed using two-tailed Pearson correlation analysis. Greenhouse-Geisser correction and *post hoc* comparisons using *t*-tests with Bonferroni correction were used. Partial eta-squared (η_p^2) values were reported for results with significant effect sizes, and the statistical significance level was set to be 0.05.

RESULTS

Craving Measures

The analysis of craving revealed a significant main effect of time point [$F(4,232) = 18.74$, $p < 0.001$, $\eta_p^2 = 0.24$], and an interaction effect of group × time point [$F(4,232) = 9.42$, $p < 0.01$, $\eta_p^2 = 0.14$]. Follow-up comparison showed that the craving of exercise group decreased from during exercise to following exercise (*p*s < 0.01). Additionally, less craving score in the exercise group (2.06 ± 1.76) relative to control group (3.40 ± 2.96) was observed during exercise time point ($p = 0.04 < 0.05$, see **Figure 2**).

Behavioral Data

In the heroin-related Go/No-Go task, regarding Go-RT, only the main effects of the time point [$F(1,58) = 76.39$, $p < 0.001$, $\eta_p^2 = 0.57$] and condition [$F(1,58) = 4.20$, $p = 0.045 < 0.05$, $\eta_p^2 = 0.07$] were revealed. No other effects were observed (see **Table 2**).

Regarding Go accuracy, neither main effects nor interaction effects were observed (see **Table 2**).

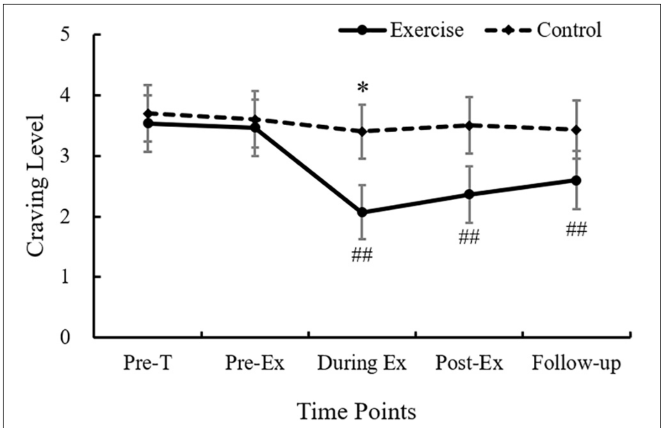

FIGURE 2 | Craving level alterations before test, before exercise, during exercise, immediately after exercise, and 60 min after exercise in two groups. *Represents a significant difference between exercise and control group, $p < 0.05$. ##represents craving at this time point is less than that at pre-task and pre-exercise in exercise group, $p < 0.01$.

Regarding No-Go accuracy, a main effect of time point [$F(1,58) = 14.99$, $p < 0.001$, $\eta_p^2 = 0.21$] and a marginal three-way interaction effect of time point × condition × group [$F(1,58) = 3.54$, $p = 0.06$, $\eta_p^2 = 0.06$] were observed. Follow-up analysis indicated that greater accuracies in exercise group during the heroin cue No-Go and neutral cue No-Go conditions in post-test compared with pre-test were observed (*p*s < 0.001, see **Table 2** and **Figure 3**).

ERP Data

Regarding N2 latency, only a main effect of site [$F(3,174) = 5.09$, $p < 0.01$, $\eta_p^2 = 0.08$], with an earlier latency for the *Cz* site than for the *Pz* site, was observed ($p < 0.05$). Since no differences in N2 latency among groups or conditions were observed, the following statistical analysis of the ERP data is focused on the amplitude.

Regarding N2 amplitude, the main effects of site [$F(3,174) = 10.37$, $p < 0.001$, $\eta_p^2 = 0.15$] and condition [$F(3,174) = 90.39$, $p < 0.001$, $\eta_p^2 = 0.61$] were observed; importantly, the interaction effects of time point × condition × site [$F(9,522) = 4.96$, $p < 0.01$, $\eta_p^2 = 0.08$] and time point × condition × group [$F(3,174) = 3.17$, $p = 0.04 < 0.05$, $\eta_p^2 = 0.05$] were observed. Follow-up analysis revealed that the N2 amplitudes for Fz, FCz, and Cz in the neutral No-Go condition were larger during the post-test than during the pre-test (*p*s < 0.05). Moreover, the N2 amplitudes in the exercise group in the heroin No-Go and neutral No-Go conditions were larger during the post-test than during the pre-test (*p*s < 0.05). Furthermore, the N2 amplitudes were generally larger for the No-Go conditions than for the Go conditions (*p*s < 0.01, see **Table 2** and **Figure 4**).

Regarding heroin cue N2d amplitude, the main effects of time [$F(1,58) = 12.72$, $p < 0.01$, $\eta_p^2 = 0.18$] and site [$F(3,174) = 3.94$, $p < 0.05$, $\eta_p^2 = 0.06$] were observed; importantly, the interaction effect of time point × site × group [$F(3,174) = 3.43$, $p < 0.05$, $\eta_p^2 = 0.06$] was observed. Follow-up analysis revealed that the N2d amplitudes at Fz, FCz, and Cz in the exercise group were larger during the post-test than during the pre-test (*p*s < 0.001); moreover, the N2d amplitudes at Fz, FCz, and Cz during the post-test were larger in the exercise group than in the control group (*p*s < 0.05, see **Table 2** and **Figure 5**).

Regarding neutral cue N2d amplitude, the main effects of time [$F(1,58) = 28.09$, $p < 0.001$, $\eta_p^2 = 0.33$] and site [$F(3,174) = 4.76$, $p < 0.01$, $\eta_p^2 = 0.08$] were observed; importantly, the interaction effect of time point × site × group [$F(3,174) = 5.24$, $p < 0.05$, $\eta_p^2 = 0.08$] was observed. Follow-up analysis revealed that the N2d amplitudes at Fz, FCz, and Cz in the exercise group were larger during the post-test than during the pre-test (*p*s < 0.01); moreover, the N2d amplitudes for FCz and Cz (*p*s < 0.05) and N2d amplitude at Fz ($p = 0.06$) during the post-test were larger and marginally significantly larger, respectively, in the exercise group than in the control group (see **Table 2** and **Figure 5**).

Spectral Power Data

Regarding theta 1 power, the main effects of time [$F(1,58) = 4.38$, $p < 0.05$, $\eta_p^2 = 0.07$], site [$F(3,174) = 22.19$, $p < 0.001$, $\eta_p^2 = 0.28$], and condition [$F(3,174) = 63.64$, $p < 0.001$, $\eta_p^2 = 0.52$] were observed; importantly, the interaction

TABLE 2 | Behavioral, neuroelectric, and spectral power data at channel FCz for the heroin-related Go/No-Go task during the treatment session (mean ± SD).

Variable	Exercise		Control	
	Pre-test	Post-test	Pre-test	Post-test
Heroin-Go RT (ms)	372.59 ± 50.96	348.79 ± 46.42	359.14 ± 45.41	342.36 ± 44.23
Neutral-Go RT (ms)	370.99 ± 50.32	348.51 ± 45.41	357.26 ± 45.96	341.01 ± 41.83
Heroin-Go accuracy (%)	95.90 ± 8.08	97.07 ± 5.99	98.40 ± 1.96	97.60 ± 3.61
Neutral-Go accuracy (%)	95.77 ± 8.42	96.47 ± 6.39	98.20 ± 2.25	98.13 ± 2.81
Heroin-No-Go accuracy (%)	86.07 ± 8.47	91.57 ± 6.69	89.41 ± 6.44	89.37 ± 7.05
Neutral-No-Go accuracy (%)	88.20 ± 6.37	90.87 ± 6.44	89.30 ± 6.58	90.00 ± 6.75
Amplitude (μV)				
Heroin-Go-N2	−4.00 ± 3.41	−3.40 ± 3.87	−4.18 ± 3.40	−3.72 ± 3.22
Heroin-No-Go-N2	−6.92 ± 4.41	−8.08 ± 5.33	−7.08 ± 3.38	−6.67 ± 3.77
Heroin-N2d	−4.61 ± 3.04	−6.78 ± 3.90	−4.52 ± 2.79	−4.53 ± 3.66
Neutral-Go-N2	−3.72 ± 3.62	−3.02 ± 4.10	−3.76 ± 3.60	−3.31 ± 2.92
Neutral-No-Go-N2	−6.48 ± 4.55	−8.04 ± 5.37	−6.25 ± 3.61	−6.72 ± 3.74
Neutral-N2d	−4.33 ± 2.59	−7.05 ± 3.39	−4.28 ± 3.17	−5.16 ± 3.67
Latency (ms)				
Heroin-Go-N2	249.63 ± 43.12	246.27 ± 46.06	264.70 ± 60.21	264.70 ± 55.86
Heroin-No-Go-N2	254.13 ± 28.03	249.20 ± 21.67	253.57 ± 25.21	251.70 ± 28.57
Heroin-N2d	259.06 ± 29.85	257.80 ± 23.53	262.23 ± 28.82	267.03 ± 40.58
Neutral-Go-N2	251.77 ± 46.63	253.80 ± 51.61	271.70 ± 67.17	259.37 ± 53.16
Neutral-No-Go-N2	255.23 ± 27.50	248.67 ± 20.53	255.27 ± 28.24	250.70 ± 27.03
Neutral-N2d	264.70 ± 36.03	264.27 ± 32.79	266.37 ± 36.50	257.26 ± 26.14
Theta 1 power (4–6 Hz; μV^2)				
Heroin-Go	2.08 ± 1.37	2.41 ± 1.58	2.04 ± 1.61	2.34 ± 1.80
Heroin-No-Go	4.37 ± 2.72	4.95 ± 2.69	3.66 ± 2.20	4.53 ± 2.51
Neutral-Go	2.08 ± 1.34	2.48 ± 1.62	2.01 ± 1.37	2.14 ± 1.79
Neutral-No-Go	4.24 ± 2.63	4.86 ± 3.14	4.01 ± 2.23	4.23 ± 2.81
Theta 2 power (6–8 Hz; μV^2)				
Heroin-Go	1.33 ± 0.83	1.64 ± 1.31	1.20 ± 0.90	1.19 ± 0.73
Heroin-No-Go	2.00 ± 1.18	2.68 ± 1.54	1.97 ± 1.14	1.80 ± 0.99
Neutral-Go	1.15 ± 0.70	1.41 ± 1.14	1.07 ± 0.51	1.26 ± 0.73
Neutral-No-Go	1.96 ± 0.96	2.59 ± 1.71	1.85 ± 1.21	2.07 ± 0.89

effect of time point × site × condition [$F(9,522) = 2.74$, $p < 0.05$, $\eta_p^2 = 0.05$] was observed. Follow-up analysis revealed that the theta 1 power outputs at Fz, FCz, and Cz in the heroin No-Go condition were larger during the post-test than during the pre-test (ps < 0.05), and the theta 1 power outputs at Fz, FCz, and Cz were larger in the No-Go condition than in the Go condition (ps < 0.001).

Regarding theta 2 power, the main effects of time [$F(1,58) = 9.89$, $p < 0.001$, $\eta_p^2 = 0.15$], site [$F(3,174) = 33.45$, $p < 0.001$, $\eta_p^2 = 0.37$], and condition [$F(3,174) = 39.31$, $p < 0.001$, $\eta_p^2 = 0.40$] were observed; importantly, a marginally significant interaction effect of time point × site × condition × group [$F(9,522) = 1.75$, $p = 0.07$, $\eta_p^2 = 0.03$] was observed. Follow-up analysis revealed that the theta 2 power outputs for Fz, FCz, and Cz in the heroin No-Go condition during the post-test were larger in the exercise group than in the control group (ps < 0.05); in addition, the theta 2 power outputs for Fz, FCz, and Cz for all groups and times were larger during the No-Go condition than during the Go condition (ps < 0.05). Furthermore, the theta 2 power outputs for Fz, FCz, and Cz for all conditions in the exercise group were larger during the post-test than during the pre-test (ps < 0.05, see **Table 2** and **Figure 6**).

Correlational Analyses

The magnitude of ΔVAS was significantly correlated with ΔN2d amplitude ($r = 0.284$, $p = 0.03 < 0.05$), but it was negatively correlated with ΔNo-Go accuracy ($r = -0.265$, $p = 0.04 < 0.05$) and Δtheta 2 power ($r = -0.282$, $p = 0.03 < 0.05$) (see **Figure 7**).

DISCUSSION

Acute Aerobic Exercise Reduces Heroin Cravings

Our study provides strong evidence that acute aerobic exercise with vigorous intensity affects heroin cravings and heroin-related inhibitory control, as determined by behavioral and neuroelectric measurements. We found that heroin cravings began to significantly decrease during aerobic exercise, and this effect persisted for 40 min after exercise. These findings are similar to those in a prior study that observed reduced cravings

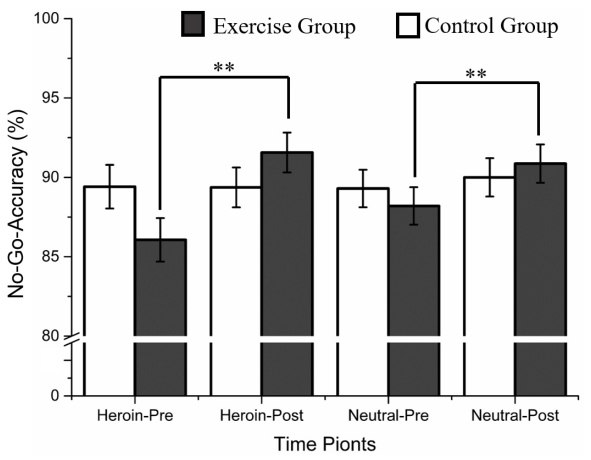

FIGURE 3 | Accuracy of heroin-related Go/No-Go task as a function of group and time point. **Represents a significant difference between pre- and post-test in heroin cue No-Go and neutral cue No-Go condition, $p < 0.01$.

for opiates in patients undergoing methadone maintenance treatment after 20 min of acute aerobic exercise with vigorous intensity (Bailey et al., 2011). Moreover, a similar effect of acute aerobic exercise with vigorous intensity on cravings has been observed in other types of addicts [i.e., methamphetamine addicts (Wang et al., 2016) and smokers (Everson et al., 2008; Scerbo et al., 2010)]. In summary, acute aerobic exercise with vigorous intensity can be used to treat heroin addicts and other types of addicts to ameliorate cravings.

There are different opinions about the underlying mechanisms by which aerobic exercise reduces the cravings of heroin addicts. Many researchers believe that these beneficial effects may be attributable to physiological and neurobiological mechanisms, in which aerobic exercise activates and modulates the neurotrophic factors (i.e., brain-derived neurotrophic factor) associated with addiction (Pareja-Galeano et al., 2013). However, this gene transcription may not occur synchronously in an acute aerobic exercise intervention (Tsai et al., 2014; Chang et al., 2017). Another plausible explanation is that acute aerobic exercise alters heroin addicts' emotions and induces stress to improve performance, which reduces cravings (Everson et al., 2008; Scerbo et al., 2010). However, individual emotions and stress are actually regulated by advanced cognitive function (i.e., executive function) (Heatherton and Wagner, 2011; Volkow et al., 2016). Combining these explanations of psychological mechanisms and the current theory of executive dysfunction in heroin addicts, we deduce that cognitive function (i.e., inhibitory control) may play an important role in the process of reducing heroin cravings.

Acute Aerobic Exercise and Inhibitory Control: Behavioral Measures

The behavioral data demonstrate that participants' accuracy during the Go/No-Go task with heroin and neutral cues improves in the No-Go condition, but not in the Go condition, following acute aerobic exercise. The findings are similar to those in a

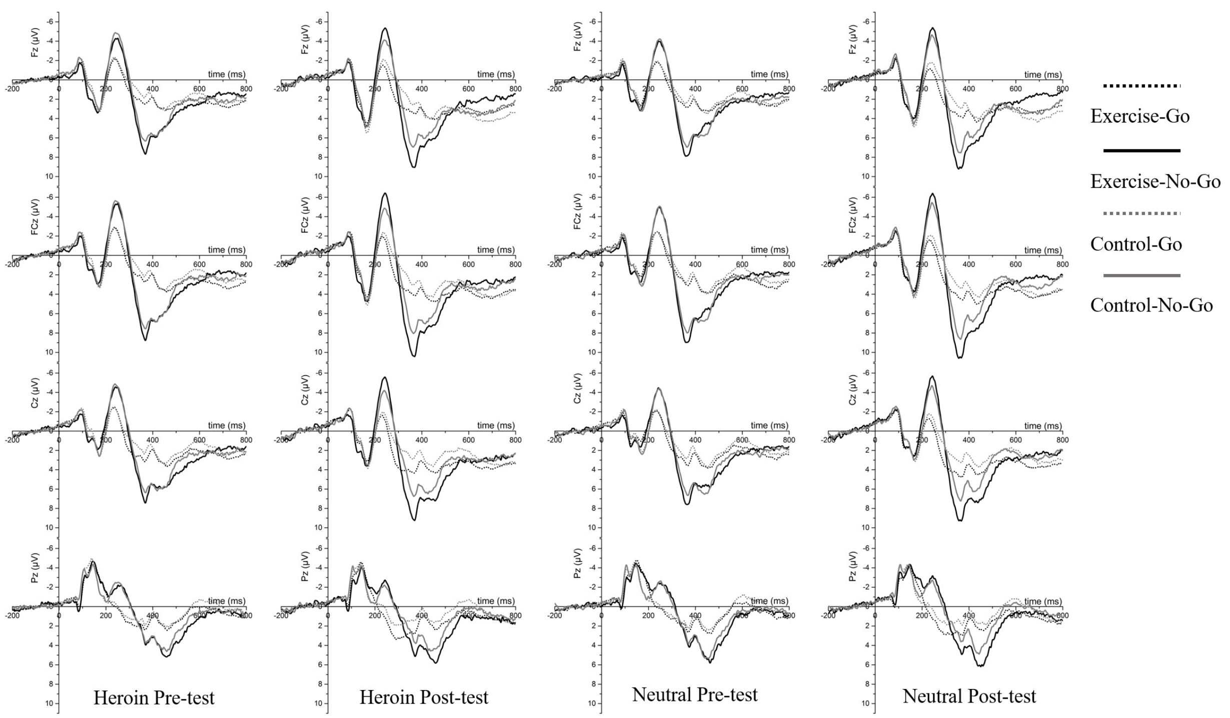

FIGURE 4 | Grand average ERPs between exercise group (Black) and control group (Gray) at Fz, FCz, Cz, and Pz for Go trials (Dot lines) and No-Go trials (Solid lines) for four tests: Heroin cue pre- and post-test and Neutral cue pre- and post-test.

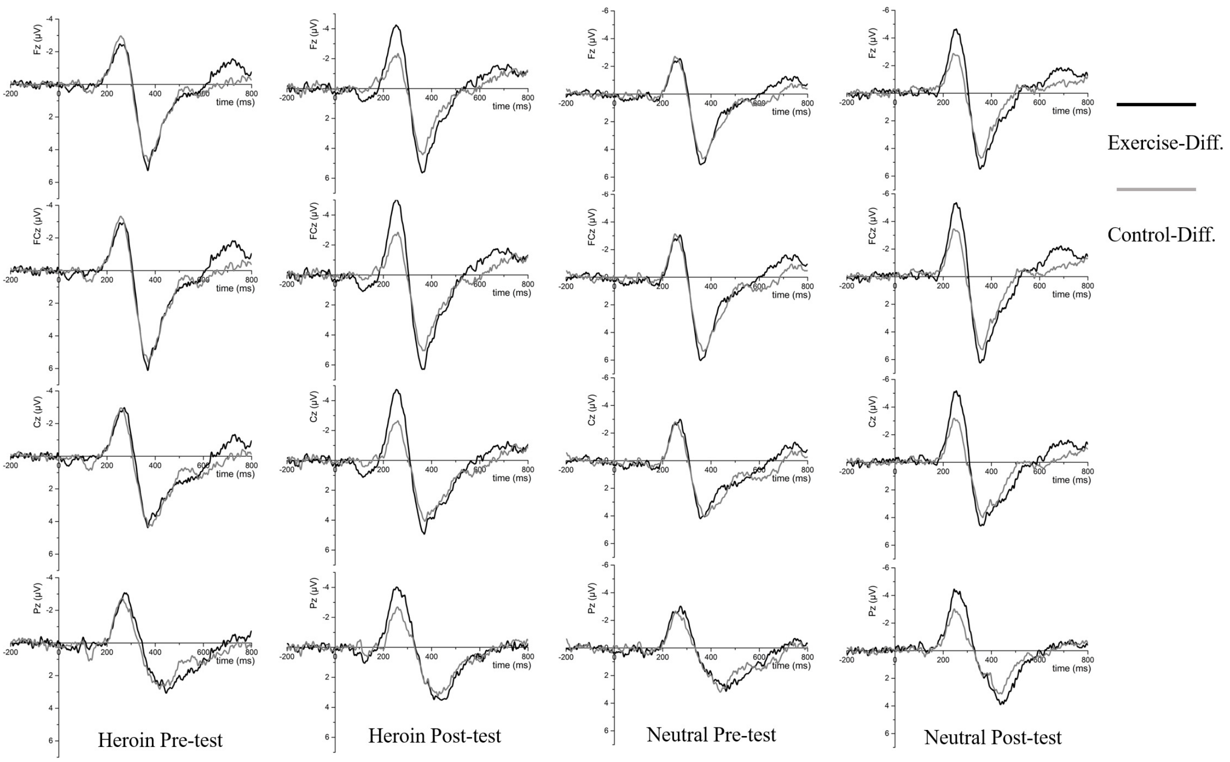

FIGURE 5 | The difference waveforms between No-Go and Go ERPs in exercise and control groups for four tests: Heroin cue pre- and post-test and Neutral cue pre- and post-test, respectively.

prior study showing that acute aerobic exercise improves the No-Go accuracy of methamphetamine addicts (Wang et al., 2015, 2016). Additionally, no significant differences were observed between heroin cues and neutral cues in terms of the No-Go task accuracy in the post-test. This finding suggests that acute aerobic exercise indiscriminately promotes inhibitory control in both general situations and heroin cue situations. Beneficial effects of acute aerobic exercise for inhibitory control in cognitive dysfunction individuals have been reported in prior studies (Chang et al., 2014; Chuang et al., 2015). This evidence also confirms that acute aerobic exercise has a positive effect on inhibitory control in heroin addicts. Interestingly, the current study demonstrates that ΔVAS is negatively correlated with ΔNo-Go accuracy ($r = -0.265$). This result preliminarily suggests that acute aerobic exercise is strongly related with improvement in inhibitory control and reductions in heroin cravings in heroin addicts. Because inhibitory control dysfunction is an important predictor of successful detoxification (Parvaz et al., 2011; Garavan and Weierstall, 2012), these behavioral measurement findings are very valuable.

Acute Aerobic Exercise and Inhibitory Control: ERP Measures

The N2 amplitudes were larger in the No-Go conditions than in the Go conditions in both groups and at both time points, indicating that the conflict monitoring system was activated and that our experimental procedure was successful. Interestingly, the N2 amplitudes for both the heroin cues and neutral cues in the No-Go condition in the exercise group, particularly in the anterior cortex, were larger after exercise than those before exercise. Moreover, the N2d amplitudes were larger in the exercise group than in the control group in fronto-central scalp regions with both the heroin cues and neutral cues in the No-Go conditions during the post-test, and the N2d amplitudes were larger during the post-test than during the pre-test in the exercise group. Accordingly, N2d amplitude more clearly characterizes the beneficial effect of aerobic exercise on inhibitory control in heroin addicts than does N2 amplitude. The No-Go N2 (and N2d) amplitude has been considered a critical indicator of conflict monitoring in the early stages of inhibitory control (Falkenstein, 2006; Folstein and Van Petten, 2008). In fact, an increase in the No-Go N2 amplitude is also considered a critical indicator of successful rehabilitation (Yang et al., 2015). It is encouraging that a correlation between ΔVAS and ΔN2d amplitude was observed in the current study ($r = 0.284$). These findings indicate that acute aerobic exercise is related to reductions in cravings and improvements in inhibitory control among heroin addicts. Accordingly, improvements in inhibitory control due to aerobic exercise may be an important mechanism by which heroin cravings decrease.

A systematic review suggested that hypoactivation of some brain regions, such as the ACC, IFG, DLPFC, and inferior regions, is associated with inhibitory control abnormalities

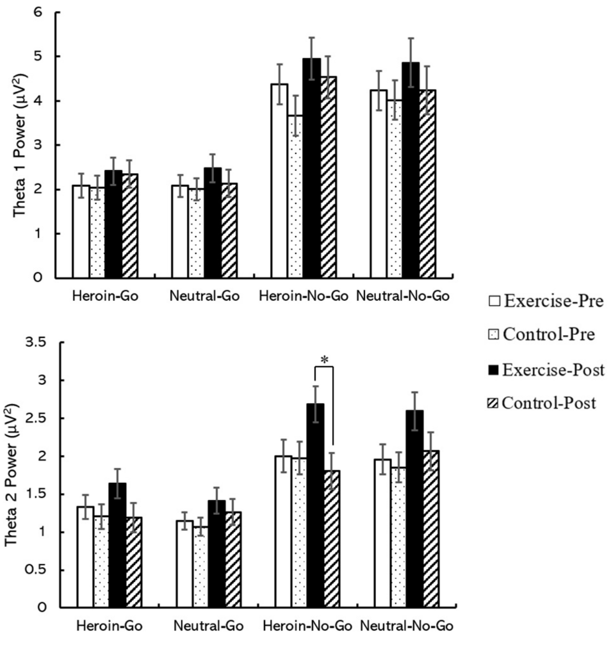

FIGURE 6 | The spectral powers of FCz site between the exercise group and the control group in the heroin-related Go/No-Go task. *Represents a significant difference between exercise group and control group in post-test in heroin cue No-Go condition, $p < 0.05$.

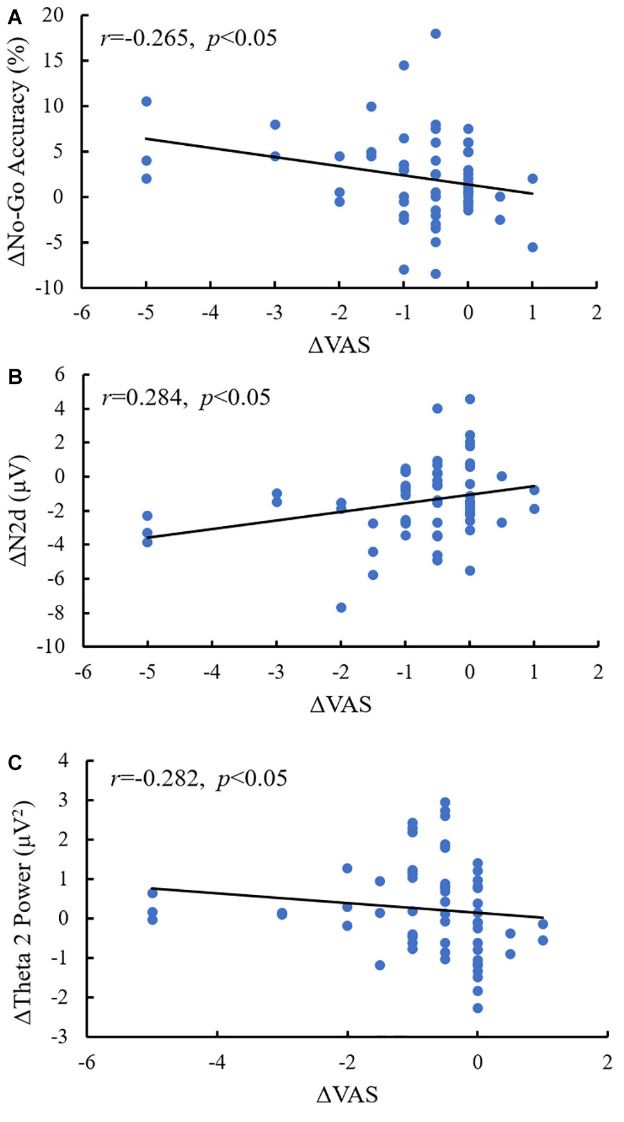

FIGURE 7 | Scatter plots for the correlation. **(A)** Correlation between ΔNo-Go accuracy and ΔVAS; **(B)** correlation between ΔN2d amplitude and ΔVAS; and **(C)** correlation between Δtheta 2 power and ΔVAS.

in individuals with drug addiction (including heroin addicts) (Simmonds et al., 2008). Fortunately, recent imaging studies have reported that acute aerobic exercise can enhance the activation of the DLPFC (Yanagisawa et al., 2010) and ACC (Fontes et al., 2015; Weng et al., 2017; Kim et al., 2018), suggesting that the increase in No-Go N2 (and N2d) amplitude observed in the current study can be interpreted as an external manifestation of aerobic exercise that activates these brain regions. Accordingly, we can conclude that an acute aerobic exercise intervention for heroin addicts can enhance the activation of cerebral cortexes associated with inhibitory control and functional disruption due to heroin consumption and improve the control of reckless impulses that heroin addicts tend to act upon without regard to the potentially catastrophic consequences (Baler and Volkow, 2006). This concept may be a plausible cognitive neurological mechanism by which aerobic exercise reduces heroin cravings.

Acute Aerobic Exercise and Inhibitory Control: Spectral Power Measures

The results regarding theta 2 band spectral power revealed patterns similar to those associated with acute aerobic exercise in behavioral and N2 amplitude results. The theta 2 band spectral power outputs, particularly in the midfrontal region, were larger during the post-test than during the pre-test, in the No-Go condition with heroin cues than in the No-Go condition with neutral cues, and in the exercise group than in the control group. The exciting findings were that the Δtheta 2 spectral power was negatively correlated with ΔN2d amplitude ($r = -0.314$) and ΔVAS ($r = -0.282$) and positively correlated with ΔNo-Go accuracy ($r = 0.440$). Previous studies have suggested that increased frontal midline theta power in the No-Go condition reflects stronger inhibitory control with the Go/No-Go paradigm (Cavanagh and Frank, 2014; Harper et al., 2014; Nguyen et al., 2017), and source imaging studies have indicated that the ACC is a primary neural generator of theta-band spectral power-related No-Go N2 components (Cohen and Cavanagh, 2011; Pandey et al., 2012; Gu et al., 2019). Accordingly, the increased effects of theta 2 spectral power once again demonstrate that improvements in inhibitory control play an important role in the process by which aerobic exercise reduces heroin cravings. Unexpectedly, no significant effects of aerobic exercise on theta 2 were observed in the post-test neutral cue condition. This result may suggest that aerobic exercise is more sensitive in improving inhibitory control with heroin cues than with neutral cues. Similar trends were also exhibited in the N2d amplitude in the post-test. The findings of spectral power once again suggest that the alpha and theta bands are relevant to the Go/No-Go paradigm, and it also implies that theta 2 band spectral power is a sensitive indicator of inhibitory control in heroin addicts.

Limitations and Future Research

To the best of our knowledge, this is the first investigation about aerobic exercise facilitating inhibitory control in heroin addicts in which behavioral and neuroelectric measures were reported. However, the results of the current study, which may be useful for future studies, should be interpreted carefully with regard to the limitations. First, the participants were recruited from the Isolated Detoxification Center and were forced to withdraw from heroin use for approximately 1 year. However, the findings from this cohort are used to guide other heroin addicts who are taking drugs, and long-term withdrawals may have certain risks due to the varying levels of brain functional impairment across participants (Rapeli et al., 2006). Future research should pay more attention to the matching of withdrawal characteristics and exercise intensity. Second, it may be risky to generalize these findings from male participants to females in heroin addict groups because sex-based differences in cravings and cognitive dysfunction have been reported (Lynch et al., 2017; Becker and Chartoff, 2019). Future research is necessary to explore the effects of aerobic exercise on cravings and inhibitory control in female heroin addicts. Third, although an attenuation in the effects of acute aerobic exercise on heroin cravings was observed 40 min after exercise, it was not possible to accurately determine the time-course effects without any attenuation of the effect of exercise. Therefore, future research should be conducted to determine the functional relationship between exercise duration and effects in heroin addicts. Last, although the effects of acute aerobic exercise may be similar to those of chronic aerobic exercise, there are differences between these types of exercise in the influences, mechanisms, and implications (Li et al., 2017; Swatridge et al., 2017), and the effects of chronic aerobic exercise on heroin cravings and inhibitory control in heroin addicts should be investigated in future research.

CONCLUSION

The present study provides new evidence to support the view that acute aerobic exercise with vigorous intensity can attenuate heroin cravings and facilitate inhibitory control. Moreover, this beneficial effect of acute aerobic exercise continued for 40 min after exercise. Furthermore, the effects of aerobic exercise on inhibitory control were reflected not only in the behavioral index (i.e., No-Go accuracy) but also in the sensitivity of the electrophysiological indicators (i.e., N2d amplitude and theta 2 spectral power) relevant to early conflict monitoring. The results of this study provide a theoretical basis for future research addressing the effects of chronic aerobic exercise on the craving and cognitive function of heroin addicts.

DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article/**Supplementary Material.**

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

DW and CZ conceptualization and funding acquisition. DW and TZ methodology. TZ software. YL and JC investigation. JC data curation. DW, TZ, and Y-KC writing—original draft preparation. DW and Y-KC writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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SUPPLEMENTARY MATERIAL

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Optimizing Sleep in Older Adults: Where Does High-Intensity Interval Training Fit?

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The present community-based study evaluated the effect of three different exercise interventions on sleep quality. Older adults were enrolled in one of three exercise intervention groups: high-intensity interval training (HIIT; $n = 20$), moderate-intensity continuous training (MICT; $n = 19$) or stretching (STRETCH; $n = 22$). Prior to and following the intervention, sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI). The PSQI was used to classify participants as poor (global PSQI score ≥5) or good (global PSQI score >5) sleepers and the effect of the intervention was examined on poor sleepers only. Around 70% of our sample was classified as poor sleepers. Poor sleepers were significantly impaired across all PSQI components, except for the use of sleeping medication, such that neither group was heavily prescribed. Exercise improved sleep quality for poor sleepers, but the intensity mattered. Specifically, MICT and STRETCH improved sleep efficiency for poor sleepers, whereas HIIT did not ($p < 0.05$). The results suggest that both MICT and STRETCH may be more effective than HIIT for optimizing sleep in poor sleepers. These findings help to inform exercise guidelines for enhancing sleep in the aging population.

Keywords: aging, exercise, sleep quality, sleep efficiency, physical health, mental health

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INTRODUCTION

Sleep is vital for optimal health (Reid et al., 2006), but its quality declines with age (Espiritu, 2008) and this increases the risk of morbidity and mortality (Henderson et al., 1995; Foley et al., 1999; Dew et al., 2003). Aerobic exercise is a potential strategy for improving sleep quality in older adults (Youngstedt, 2005; Yang et al., 2012; Kredlow et al., 2015; Bonardi et al., 2016), especially for those with pre-existing sleep impairments (i.e., poor sleepers; King et al., 1997, 2008; Tworoger et al., 2003; Passos et al., 2011; Yang et al., 2012). However, it remains unclear whether all types of exercise confer similar benefits on sleep.

Much of the research in this field has focused on moderate-intensity continuous training (MICT), demonstrating beneficial effects on both objective and subjective measures of sleep quality (King et al., 1997, 2008; Tworoger et al., 2003; Passos et al., 2011; Yang et al., 2012). With respect to objective measures, a 12-month moderate-intensity aerobic exercise intervention with older adults found significant changes in sleep architecture compared to controls, with less time spent in Stage 1 sleep, more time in Stage 2 sleep, and overall fewer awakenings during the first third of the sleep period (King et al., 2008). With respect to subjective measures, older adults report improvements on various aspects of the Pittsburgh Sleep Quality Index (PSQI) following MICT, including the global PSQI sleep score, sleep quality, sleep onset latency, sleep disturbance, and sleep duration (King et al., 1997, 2008). Thus, there is accumulating evidence that MICT improves sleep in older adults, but more work is needed to investigate other modalities of exercise and refine the optimal exercise prescription for promoting sleep in the aging population.

High-intensity interval training (HIIT) is a popular alternative to traditional MICT in young and older adults. Compared to MICT, HIIT produces similar-to-superior improvements in physiology and cognition in older adults (Wisløff et al., 2007; Coetsee and Terblanche, 2017), with the added benefit of requiring less time. With respect to sleep outcomes, an *acute* bout of high-intensity exercise may be equally effective at optimizing sleep as moderate intensity exercise (Kredlow et al., 2015). However, a recent meta-analysis was unable to examine the effects of *chronic* high-intensity exercise training on sleep due to insufficient evidence (Kredlow et al., 2015). To our knowledge there has only been one study investigating the effect of HIIT on sleep quality (Adams et al., 2018). This was a 12-week exercise intervention conducted with testicular cancer survivors and found no improvements in sleep quality (Adams et al., 2018). More work is clearly needed to understand whether a regular program of HIIT provides similar or greater benefits compared to MICT for sleep promotion.

In addition to aerobic exercise, stretching has been considered a potential strategy for improving sleep in older adults (King et al., 1997; Morin et al., 1999; Tworoger et al., 2003). One study found that both aerobic exercise and stretching improved sleep quality in postmenopausal women (Tworoger et al., 2003). Although most research examining the effects of exercise on brain health use stretching as a control, in the context of sleep, stretching does not function as a true control because of its potential to influence sleep, possibly through physical relaxation (King et al., 1997), and thus represents another viable modality of exercise for improving sleep in older adults.

The current study examined the effects of exercise type on sleep quality in older adults. This study used archival data from a community-based study that examined the role of exercise intensity on cognition in older adults (Kovacevic et al., 2019). Sedentary but otherwise healthy older adults over the age of 60 years were recruited to participate in this study. Participants were assigned to one of three intervention groups: HIIT, MICT, or a stretching (STRETCH) group. Sleep quality was assessed using the PSQI. We hypothesized that MICT would be effective at improving sleep quality but were unclear whether HIIT or STRETCH would confer similar benefits. As a secondary analysis, we split participants into poor and good sleepers using the PSQI, with particular interest in identifying interventions that benefit the poor sleepers. The impact of the interventions on cardiorespiratory fitness, body mass index (BMI), as well as measures of psychological stress, and global cognition were also examined.

MATERIALS AND METHODS

Participants

This community-based study took place over a period of 2.5 years from August 2014 to March 2017. The methodology was reported by Kovacevic et al. (2019). Participants were recruited on a rolling basis throughout the study period through local news outlets and postings. Participants consisted of sedentary, but otherwise healthy community-dwelling older adults over the age of 60 years. Participants were excluded from the study if they reported engaging in more than 1 h of vigorous physical activity per week or if they had a known diagnosis of cognitive impairment. Participant eligibility was assessed through verbal or written confirmation *via* phone or email. Participants were also required to complete a stress test with their physician prior to enrolment to screen for any abnormal response to exercise. Those with abnormal responses to exercise were deemed ineligible. Eligible participants provided written informed consent and received $40 for participation upon study completion. This study received ethics clearance from the Hamilton Integrated Research Ethics Board.

Procedure

The procedure consisted of pre and post-intervention assessments, separated by a 12-week intervention. The pre and post-intervention assessments included measures of sleep quality, as well as physical health, stress, and cognition. Post-intervention testing was completed within 48 h of the final intervention exposure.

Figure 1 displays the flow of participants through the study. A total of 83 participants enrolled in the study. Of those 83 participants, five participants withdrew before beginning training (HIIT: n = 4, MICT: n = 1) and 13 participants discontinued the intervention (HIIT: n = 3, MICT: n = 5, STRETCH: n = 5). A total of 65 participants completed the intervention. However, one participant in the MICT group was excluded from analysis due to a diagnosis of cognitive impairment prior to study completion and three participants did not complete the PSQI at baseline (HIIT: n = 1, MICT: n = 1, STRETCH: n = 1). Thus, the current sample is comprised of 61 participants. Participants trained in one of the three groups for the duration of the intervention: (1) HIIT (n = 20), (2) MICT (n = 19), or (3) STRETCH (n = 22). Group assignment was performed by a researcher and was done according to blocks stratified by sex to ensure equal distribution among groups. Group sizes were limited due to equipment availability, thus in the event that a group was full participants were assigned to the next available group. Group assignment took place prior to the pre-intervention assessment, but participants were not informed of their group placement until pre-intervention assessments were completed.

Pre and Post-intervention Assessments

Sleep

Participants completed the 19-item PSQI to assess subjective sleep quality during the last month (Buysse et al., 1989). The primary measures of sleep quality derived from the PSQI were sleep duration and sleep efficiency. Data were screened to ensure sleep efficiency did not exceed 100%. Sleep duration was defined as the hours of sleep per night. Sleep efficiency was calculated using the following formula:

$$Sleep\ efficiency = \left(\frac{number\ of\ hours\ slept}{number\ of\ hours\ spent\ in\ bed} \right) \times 100$$

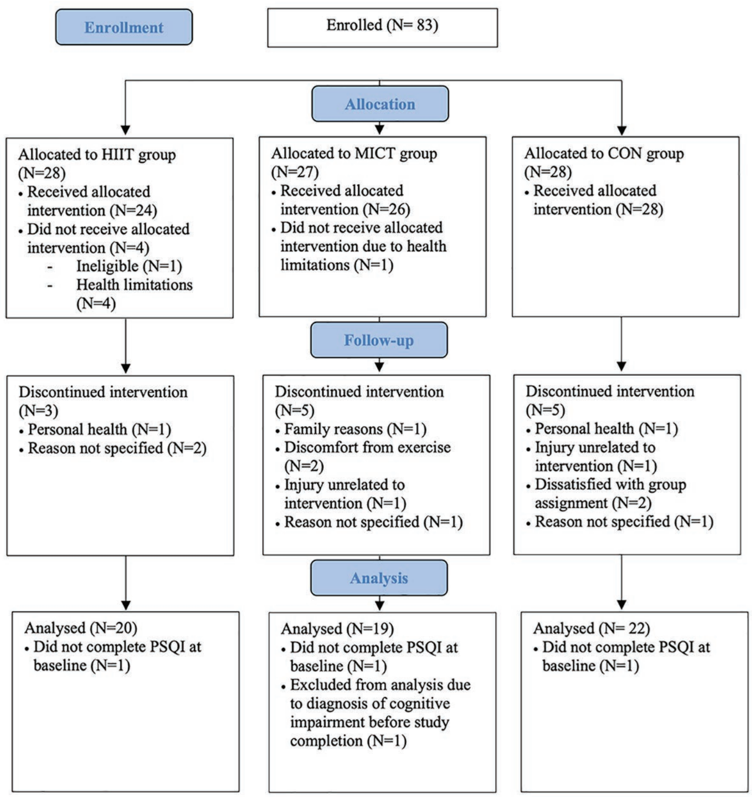

FIGURE 1 | Flow of participants through study (Kovacevic et al., 2019).

The 19 items on the PSQI were also combined to create seven component scores (range 0–3): (1) subjective sleep quality, (2) sleep latency, (3) sleep duration, (4) habitual sleep efficiency, (5) sleep disturbances, (6) use of sleeping medication, and (7) daytime dysfunction. The sum of the seven component scores yields a global score of sleep quality (range 0–21). Higher scores indicate worse sleep, with a cut-off score of 5 indicating clinical sleep impairment (Buysse et al., 1989).

Psychological Stress

The Perceived Stress Scale (PSS) was used to assess the participants' perception of their psychological stress during the last month. This 10-item questionnaire measures the degree to which situations are considered stressful, where a higher score on the PSS is indicative of greater perceived stress (Cohen et al., 1983).

Global Cognition

The Montreal Cognitive Assessment (MoCA) was used to assess global cognition. The maximum score on the MoCA is 30, with higher scores indicating better cognitive function (Nasreddine et al., 2005).

Cardiorespiratory Fitness

Participants completed the modified Bruce protocol on a motor driven treadmill (Life Fitness 95Ti), with stages of 3 min in duration, as a predictive test of peak oxygen uptake (VO_2 peak). The modified Bruce protocol introduced an adaptation phase of 6 min at the beginning of the test (Willemsen et al., 2010), while the remainder of the assessment followed the standard Bruce protocol (Sheffield and Roitman, 1976; Willemsen et al., 2010). A trained member of the research team supervised the test and recorded time at exhaustion, heart rate (HR) at each interval and at exhaustion (measured using Polar FT1 HR monitors), and rating of perceived exertion (RPE) at each interval using the Borg 6-to-20 scale (Borg, 1982). The test was terminated upon volitional exhaustion or presentation of abnormal symptoms. Predicted VO_2 peak was calculated using the equation below, with a weighting factor of one for men and two for women (Bruce et al., 1973). The 6-min adaptation phase from the modified Bruce protocol was not included in this calculation.

$$Predicted\ VO_2\ peak = 6.70 - 2.82(weighting\ factor\ for\ sex) + 0.056(duration\ in\ seconds)$$

Prior to completing the cardiorespiratory fitness assessment, participants were familiarized with the treadmill and completed the first 9.5 min (the first 3 stages) of the modified Bruce protocol, unless volitional exhaustion was reached earlier. Midway through training, an additional cardiorespiratory fitness assessment was completed to reassess peak heart rate (HR peak) and increase the difficulty of exercise training accordingly.

The first 10 participants that enrolled in the study completed the Single Stage Treadmill Walking Test (Ebbeling et al., 1990), instead of the modified Bruce protocol, as the pre-intervention cardiorespiratory fitness assessment. The modified Bruce protocol was subsequently used for all participants upon ethics approval. Participants who completed the Single Stage Treadmill Walking Test were excluded from analysis of cardiorespiratory fitness.

Exercise Intervention

All groups met three times per week for the duration of the 12-week intervention and were supervised by a trained member of the research team. The 18th session was replaced with the additional cardiorespiratory fitness assessment, resulting in a total of 35 training sessions (actual completed: HIIT: 34 ± 4; MICT: 32 ± 5; STRETCH: 35 ± 2; M ± SD). Participants were instructed not to engage in additional physical activity for the duration of the study. Participants were accommodated for missed exercise sessions and continued to meet with their respective exercise groups until they achieved as close to the target of 35 training sessions as possible.

The HIIT and MICT protocols were adapted from previous work that was conducted in a sample of older adults with heart failure and thus was deemed feasible for our sample (Wisløff et al., 2007). The exercise protocols were designed to be matched for total training load and consequently their durations differed. All exercise training was completed on a motor-driven treadmill (Life Fitness 95Ti). The speed and incline of the treadmill were adjusted to elicit the target HR, which was based on the participant's HR peak achieved during the fitness assessment, and target RPE. If both target HR and target RPE were not achieved simultaneously, HR was the preferred indicator of intensity.

High-Intensity Interval Training

The total time was 43 min. Participants warmed up for 3 min at 0% grade and 50–70% HR peak. Participants then completed 10 min at 5% grade and 60–70% HR peak. Next, they began the interval protocol, which consisted of four 4-min intervals at 5% grade and 90–95% HR peak, interspersed with 3-min of active recovery at 50–70% HR peak. After that, participants cooled down for 2 min at 50–70% HR peak. HR and RPE were recorded at the end of the warm-up, as well as after each 4-min interval and 3-min of active recovery. On average across each session, the HIIT protocol elicited a HR of 125 ± 9 beats/min, corresponding to 88 ± 4% of HR peak, and an RPE of 13.1 ± 1.7 out of 20 (M ± SD).

Moderate-Intensity Continuous Training

The total time was 52 min. For the first 3 min, participants warmed up by completing 3 min at 0% grade and 50–70% HR peak. For the next 47 min, they walked continuously at 70–75% HR peak. After that, participants cooled down for 2 min at 50–70% HR peak. HR and RPE were recorded after the warm-up and every 7 min for the remainder of the session. On average across each session, the MICT protocol elicited a HR of 104 ± 12, corresponding to 75 ± 5% of HR peak, and an RPE of 9.2 ± 1.6 out of 20 (M ± SD).

Stretching

The original study investigating the effects of exercise intensity on cognition intended that the STRETCH group act as a control for the exercise treatment arms (Kovacevic et al., 2019). However, the present study treated STRETCH as an additional treatment group, given the evidence that stretching may improve sleep quality (Morin et al., 1999; Tworoger et al., 2003), possibly through relaxation (King et al., 1997). The STRETCH group completed a series of non-aerobic seated and standing stretches in a large classroom. The sessions were 30 min in duration. The stretching protocol was designed for older adults and aimed at whole-body stretching. Each stretch was held for approximately 30–40 s. RPE was recorded at the end of each session. On average, the STRETCH protocol elicited an RPE of 8.2 ± 1.7 out of 20 (M ± SD). HR was not recorded during the STRETCH protocol.

Statistical Analysis

All data was analyzed using IBM SPSS Statistics Software 25. Data were checked for extreme outliers, which were defined as values greater or less than three standard deviations (SD) from the mean. Two outliers were identified (pre-intervention PSS: STRETCH = 1; global PSQI change score: HIIT = 1). Data were then screened for missing cells; 7% of the data were missing. Outliers and missing cells were excluded pairwise. Normality was assessed using the Shapiro-Wilk test and through visual inspection of histograms.

Baseline Characteristics: Group Effects

One-way analyses of variance (ANOVAs) were conducted to determine if there were any baseline differences between groups (HIIT, MICT, and STRETCH) in age, PSQI scores (global sleep quality, sleep efficiency, sleep duration, and components one through seven), VO_2 peak, BMI, PSS, or MoCA. *Post hoc* pairwise comparisons were performed to examine group effects.

Exercise Intervention: Group Effects

To evaluate the effect of the exercise intervention on sleep quality, analyses of covariance (ANCOVAs) were conducted on PSQI change scores (post-pre) of global sleep quality, sleep efficiency, sleep duration, as well as components one through seven, with a between-subjects factor of group (HIIT, MICT, and STRETCH). Age, sex, and BMI have been reported to effect sleep quality (Redline et al., 2004; Lauderdale et al., 2009) and thus, were included as covariates in all sleep analyses. *Post hoc* pairwise comparisons were performed to examine group effects.

To evaluate the effect of the intervention on cardiorespiratory fitness, an ANCOVA was conducted on the change score (post-pre) of VO_2 peak with a between-subjects factor of group (HIIT, MICT, and STRETCH). Age and sex were included as covariates. *Post hoc* pairwise comparisons were performed to examine group effects.

Baseline Characteristics: Subgroup Effects

As a secondary analysis, we used the measure of global sleep quality to identify poor sleepers (global PSQI score ≥5) and good sleepers (global PSQI score <5; Buysse et al., 1989; Irwin et al., 2008). To characterize the sample of poor and good sleepers at baseline, we conducted ANCOVAs with a between-subjects factor of sleeper status (poor sleeper, good sleeper) on PSQI scores (global sleep quality, sleep efficiency, sleep duration, and components one through seven), with age, sex, and BMI included as covariates, as well as on VO_2 peak, BMI, PSS, and MoCA, with age and sex included as covariates.

Exercise Intervention: Subgroup Effects

Next, we evaluated the effect of the exercise intervention on sleep quality in poor sleepers only. From an intervention standpoint, poor sleepers are the target group for treatment. From a statistical standpoint, the random sample of older adults drawn for the original study examining cognition included only a small sample of good sleepers that was insufficient for comparison (HIIT: $n = 5$, MICT: $n = 4$, STRETCH: $n = 9$). For poor sleepers, ANCOVAs were conducted on PSQI change scores (post-pre) of global sleep quality, sleep efficiency, sleep duration, as well as components one through seven, with a between-subjects factor of group (HIIT, MICT, and STRETCH). Age, sex, and BMI were included as covariates. *Post hoc* pairwise comparisons were performed to examine group effects.

Cardiorespiratory Fitness and Sleep

To explore the relationship between cardiorespiratory fitness and sleep, we conducted partial correlations between VO_2 peak change scores and change scores for any sleep variable significantly affected by the intervention. Age, sex, and BMI were controlled for.

For all ANOVAs and ANCOVAs, partial eta square effect sizes are reported and can be interpreted as small (0.01), medium (0.06), and large (0.14; Miles and Shevlin, 2001).

RESULTS

Baseline Characteristics: Group Effects

Baseline characteristics are reported in **Table 1**. Prior to the intervention, there was a main effect of group on cardiorespiratory fitness [$F(2, 47) = 4.50$, $p = 0.016$, $\eta_p^2 = 0.16$], such that HIIT and MICT had significantly higher VO_2 peak at baseline than STRETCH (HIIT vs. STRETCH: $p = 0.015$; MICT vs. STRETCH: $p = 0.011$), but there was no significant difference between HIIT and MICT ($p = 0.95$). There were no significant group differences at baseline with respect to age, PSQI scores (global sleep quality, sleep efficiency, sleep duration, and components one through seven), BMI, PSS, or MoCA (all $p > 0.050$).

Exercise Intervention: Group Effects

There was no effect of the exercise intervention on global sleep quality, sleep efficiency, sleep duration, or the seven component scores (all $p > 0.050$). However, the exercise intervention induced the expected cardiorespiratory fitness adaptations [$F(2, 42) = 13.91$, $p < 0.001$, $\eta_p^2 = 0.40$], such that both HIIT and MICT yielded significantly greater improvements in VO_2 peak than STRETCH (HIIT vs. STRETCH: $p < 0.001$; MICT vs. STRETCH: $p < 0.001$), but there was no significant difference between HIIT and MICT ($p = 0.48$).

TABLE 1 | Pre and post outcome measures for the high-intensity interval training (HIIT), moderate-intensity continuous training (MICT), and stretching (STRETCH) groups.

	HIIT (*n* = 20)		MICT (*n* = 19)		STRETCH (*n* = 22)	
Age	72.4 (4.5)		72.3 (6.2)		71.1 (6.5)	
Sex (% female)	70%		47%		68%	
	Pre	Post	Pre	Post	Pre	Post
Sleep duration (hours)	6.8 (1.2)	6.8 (1.2)	6.5 (1.4)	6.7 (1.5)	7.1 (1.6)	6.8 (1.2)
Sleep efficiency (%)	80.6 (15.9)	79.7 (14.3)	78.6 (15.3)	84.2 (15.4)	73.9 (15.3)	78.5 (15.9)
Global PSQI score	7.0 (3.5)	7.3 (4.6)	7.8 (4.6)	7.6 (4.2)	6.8 (4.6)	6.2 (3.7)
Subjective sleep quality	1.1 (0.8)	1.1 (0.9)	1.3 (0.7)	1.1 (0.8)	0.8 (0.8)	0.9 (0.8)
Sleep latency	1.2 (1.1)	0.9 (0.7)	1.2 (1.1)	0.8 (0.7)	1.3 (1.1)	0.7 (0.6)
Sleep duration	0.8 (0.8)	0.8 (0.8)	1.1 (1.0)	1.0 (0.9)	0.7 (0.9)	0.9 (0.8)
Habitual sleep efficiency	0.9 (1.1)	1.2 (1.3)	1.2 (1.2)	0.8 (1.2)	1.2 (1.3)	1.0 (1.2)
Sleep disturbances	1.6 (0.5)	1.6 (0.6)	1.7 (0.6)	1.6 (0.5)	1.5 (0.6)	1.3 (0.6)
Use of sleeping medication	0.5 (0.9)	0.7 (1.1)	0.8 (1.3)	0.8 (1.3)	0.7 (1.2)	0.6 (1.0)
Daytime dysfunction	1.0 (0.6)	0.9 (0.4)	0.7 (0.7)	0.5 (0.5)	0.7 (0.6)	0.7 (0.5)
Predicted VO_2 peak (ml/kg/min)	24.8 (6.3)*	31.0 (5.6)	24.9 (5.5)*	30.7 (4.4)	19.2 (6.9)	18.3 (6.8)
BMI (kg/m^2)	27.1 (4.0)	27.4 (4.0)	28.1 (3.7)	27.9 (3.5)	29.5 (6.0)	29.7 (6.3)
PSS	13.3 (6.0)	11.8 (5.7)	14.2 (5.8)	12.6 (6.5)	13.6 (5.1)	12.3 (6.2)
MoCA	25.5 (3.1)	26.0 (2.9)	26.1 (3.1)	25.9 (3.2)	26.3 (2.5)	25.5 (2.7)

*Significantly different from STRETCH (p < 0.050).

Sex is presented as percentage of females; all other data is presented as mean (SD). ANOVAs revealed a main effect of exercise group on cardiorespiratory fitness (p = 0.016), such that HIIT and MICT had significantly higher VO_2 peak at baseline than STRETCH (HIIT vs. STRETCH: p = 0.015; MICT vs. STRETCH: p = 0.011), but there was no significant difference between HIIT and MICT (p = 0.95). BMI, Body Mass Index; MoCA, Montreal Cognitive Assessment; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale.

Baseline Characteristics: Subgroup Effects

Using the global measure of sleep quality, participants were categorized as poor (global PSQI score ≥5) or good sleepers (global PSQI score <5; Buysse et al., 1989; Irwin et al., 2008). **Table 2** displays baseline characteristics of poor and good sleepers. At baseline, poor sleepers had a significantly lower global sleep quality score than good sleepers [$F(1, 55) = 53.38$, $p < 0.001$, $\eta_p^2 = 0.49$]. Poor sleepers also had significantly shorter sleep duration [hours; $F(1, 56) = 17.47$, $p < 0.001$, $\eta_p^2 = 0.24$], worse sleep efficiency [$F(1, 50) = 18.79$, $p < 0.001$, $\eta_p^2 = 0.27$], and scored higher on six of seven PSQI component scores, including subjective sleep quality [$F(1, 55) = 34.98$, $p < 0.001$, $\eta_p^2 = 0.39$], sleep latency [$F(1, 56) = 33.72$, $p < 0.001$, $\eta_p^2 = 0.37$], sleep duration [$F(1, 56) = 22.49$, $p < 0.001$, $\eta_p^2 = 0.29$], habitual sleep efficiency [$F(1, 56) = 18.45$, $p < 0.001$, $\eta_p^2 = 0.25$], sleep disturbances [$F(1, 56) = 30.71$, $p < 0.001$, $\eta_p^2 = 0.35$], and daytime dysfunction [$F(1, 56) = 5.39$, $p = 0.024$, $\eta_p^2 = 0.09$]. There were no significant differences between poor and good sleepers for use of sleeping medication [$F(1, 55) = 3.35$, $p = 0.073$, $\eta_p^2 = 0.06$], but this trended in the same direction as the other variables. Furthermore, poor sleepers reported significantly higher perceived stress than good sleepers [$F(1, 56) = 6.07$, $p = 0.017$, $\eta_p^2 = 0.10$], but did not differ on VO_2 peak, BMI, or MoCA (all $p > 0.050$).

TABLE 2 | Baseline characteristics for poor and good sleepers.

	Poor sleepers (*n* = 43)	Good sleepers (*n* = 18)
Sleep duration (hours)	6.4 (1.2)**	7.9 (1.2)
Sleep efficiency (%)	72.8 (13.8)**	91.0 (13.8)
Global PSQI score	9.1 (3.0)**	2.6 (3.0)
Subjective sleep quality	1.3 (0.6)**	0.3 (0.6)
Sleep latency	1.6 (0.9)**	0.2 (0.9)
Sleep duration	1.2 (0.8)**	0.1 (0.8)
Habitual sleep efficiency	1.5 (1.1)**	0.2 (1.1)
Sleep disturbances	1.8 (0.4)**	1.1 (0.4)
Use of sleeping medication	0.8 (1.1)	0.3 (1.1)
Daytime dysfunction	0.9 (0.6)*	0.5 (0.6)
Predicted VO_2 peak (ml/kg/min)	22.1 (6.3)	24.6 (6.3)
BMI (kg/m²)	27.9 (4.7)	29.0 (4.8)
PSS	14.8 (5.2)*	11.1 (5.3)
MoCA	25.8 (2.8)	26.2 (2.9)

*$p < 0.050$; **$p < 0.010$.

Data are presented as mean (SD). ANCOVAs revealed that poor sleepers had significantly lower global sleep quality score than good sleepers (p < 0.001), as well as significantly shorter sleep duration (hours), worse sleep efficiency, and scored higher on six of seven PSQI component scores, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances (all p < 0.001), and daytime dysfunction (p = 0.024). Poor sleepers also reported significantly higher perceived stress than good sleepers (p = 0.017), but did not differ on use of sleeping medication, VO_2 peak, BMI, or MoCA (all p > 0.050). Sleep variables are adjusted for age, sex, and BMI. Predicted VO_2 peak, BMI, PSS, and MoCA are adjusted for age and sex. BMI, Body Mass Index; MoCA, Montreal Cognitive Assessment; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale.

Exercise Intervention: Subgroup Effects

The effects of the exercise interventions on poor sleepers are presented in **Table 3**. The exercise intervention improved sleep efficiency for poor sleepers, except for when done at a high intensity (**Figure 2**). This was supported by a main effect of group [$F(2, 29) = 3.27$, $p = 0.053$, $\eta_p^2 = 0.18$], whereby MICT and STRETCH resulted in improvements in sleep efficiency, but HIIT did not (MICT vs. HIIT: $p = 0.030$; STRETCH vs. HIIT: $p = 0.050$). MICT and STRETCH groups were not statistically different ($p = 0.94$). No other sleep measure was significantly affected by the intervention (all $p > 0.050$).

Cardiorespiratory Fitness and Sleep

There was no correlation between change in cardiorespiratory fitness and change in sleep efficiency in poor sleepers [$r(22) = -0.05$, $p = 0.81$].

DISCUSSION

The present community-based study examined the effect of exercise intensity on sleep quality in older adults. The exercise intervention had no effect on sleep when examining the entire sample of older adults. However, subgroup analyses revealed

TABLE 3 | Pre and post sleep measures for the HIIT, MICT, and STRETCH groups in poor sleepers only.

	HIIT (*n* = 15)		MICT (*n* = 15)		STRETCH (*n* = 13)	
	Pre	Post	Pre	Post	Pre	Post
Sleep duration (hours)	6.7 (1.3)	6.5 (1.2)	6.1 (1.2)	6.5 (1.5)	6.3 (1.5)	6.3 (1.3)
Sleep efficiency (%)	77.6 (16.7)	75.2 (13.7)	73.4 (13.0)	80.8 (15.1)	66.6 (13.5)	74.1 (17.3)
Global PSQI score	8.3 (2.8)	9.1 (3.9)	9.5 (3.8)	8.6 (4.0)	9.6 (4.0)	8.3 (3.6)
Subjective sleep quality	1.3 (0.7)	1.4 (0.8)	1.5 (0.6)	1.3 (0.7)	1.2 (0.7)	1.3 (0.8)
Sleep latency	1.5 (1.1)	1.1 (0.6)	1.5 (1.1)	1.0 (0.7)	1.9 (0.9)	1.0 (0.4)
Sleep duration	0.9 (0.8)	1.0 (0.8)	1.4 (0.9)	1.1 (1.0)	1.2 (0.8)	1.3 (0.8)
Habitual sleep efficiency	1.1 (1.2)	1.6 (1.2)	1.5 (1.2)	1.0 (1.2)	1.9 (1.3)	1.5 (1.3)
Sleep disturbances	1.8 (0.4)	1.7 (0.6)	1.9 (0.5)	1.7 (0.5)	1.8 (0.6)	1.6 (0.5)
Use of sleeping medication	0.7 (1.0)	0.9 (1.2)	1.0 (1.4)	1.0 (1.4)	0.8 (1.3)	0.5 (1.0)
Daytime dysfunction	1.1 (0.7)	0.9 (0.5)	0.8 (0.7)	0.6 (0.5)	0.8 (0.6)	0.8 (0.4)

Data is presented as mean (SD). PSQI, Pittsburgh Sleep Quality Index.

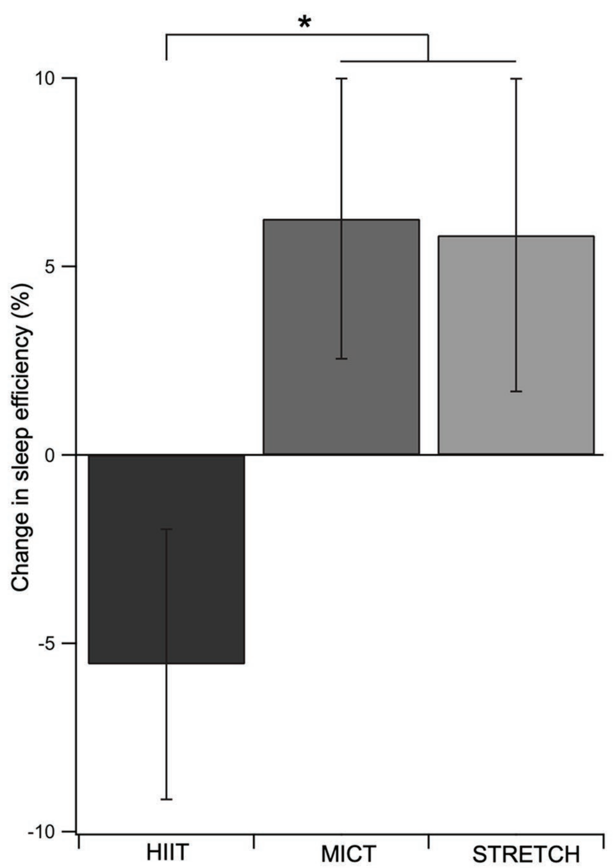

FIGURE 2 | Change in sleep efficiency as a function of exercise group in poor sleepers. Both MICT and STRETCH groups experienced greater improvements in sleep efficiency than the HIIT group. This was supported by an ANCOVA, which revealed a main effect of group for sleep efficiency. Age, sex, and body mass index were included as covariates. Error bars represent SEM for each group. $^*p \leq 0.05$.

that among poor sleepers, both MICT and STRETCH improved sleep efficiency, whereas HIIT did not.

The majority of the community-dwelling older adults in our sample were classified as poor sleepers. These poor sleepers were significantly impaired across all PSQI components except for the use of sleeping medication, whereby neither group were heavily prescribed. These results highlight the prevalence and extent of sleep impairments among older adults in the community. The low endorsement of sleep medication by poor sleepers may signify a lack of medical support for their impairment. If untreated, impaired sleep can disrupt many aspects of health and accelerate age-related decline (Foley et al., 1999; Dew et al., 2003; Reid et al., 2006). Indeed, our poor sleepers also had higher levels of psychological stress than good sleepers. Although the present results cannot speak to whether this was a cause or consequence of poor sleep, prior research suggests it can be both; poor sleep creates more psychological stress, which in turn can further shorten sleep duration and impair sleep quality (Åkerstedt, 2006). Unfortunately, this creates a negative feedback loop to perpetuate sleep impairments. Within this context, the results point to a critical need for effective interventions to help older adults manage sleep.

Our results support the accumulating evidence that exercise in the form of MICT improves sleep in older adults (King et al., 1997, 2008; Tworoger et al., 2003; Passos et al., 2011). However, this was only seen among those with poor sleep quality. Indeed, it has been suggested that good sleepers are unlikely to exhibit large improvements in sleep following an exercise intervention due to ceiling effects (Youngstedt, 2003, 2005), providing a potential explanation for why we did not find an effect of exercise on sleep when examining all older adults (i.e., both good and poor sleepers). The novel contribution here was contrasting MICT with HIIT – a popular alternative form of aerobic exercise. At the group level, HIIT was not effective at improving sleep efficiency in poor sleepers, while MICT was. These findings suggest there may be an intensity threshold for the sleep-promoting effects of exercise, such that exercise at a high intensity could be harmful to sleep. Indeed, high-intensity exercise may elicit heightened physiological arousal and muscle soreness, counteracting the potential beneficial effects of exercise on sleep and tipping the balance toward inhibiting, rather than promoting, sleep (Borbély, 1982; Driver and Taylor, 2000; Fuller et al., 2006).

Despite the potential for exercise to promote sleep, the underlying mechanisms are not fully understood (Uchida et al., 2012; Kredlow et al., 2015). One proposed mechanism is that exercise-induced improvements in cardiorespiratory fitness promote sleep (Shapiro et al., 1984). Our results do not lend support for this proposed mechanism. Instead, we found no relationship between change in fitness and change in sleep efficiency among the poor sleepers. Furthermore, sleep efficiency improved in the STRETCH group despite no change in cardiorespiratory fitness. These findings suggest the sleep-promoting effects of exercise may be driven by changes in other physiological or psychological variables, such as increased energy consumption and metabolic rate (Morselli et al., 2012) or changes in mood (Buman and King, 2010). Future research is needed to elucidate the underlying mechanisms through which exercise improves sleep in older adults to help further refine implementation.

While this study makes important contributions to our understanding of the relationship between exercise intensity and sleep quality in older adults, it is not without its limitations. Firstly, this was a community-based study with a focus on feasibility and implementation, and as a result did not meet all requirements for a clinical trial. Secondly, the STRETCH group in this study was originally designed to control for the social factors associated with participating in an exercise intervention that are known to affect cognition (the main focus of the original study; Kovacevic et al., 2019). However, stretching improves sleep (**Figure 2**), possibly through physical relaxation (King et al., 1997), and therefore is not the ideal control condition for sleep outcomes. Thus, we treated the STRETCH group as an additional treatment group and did not have a control group. Follow up studies should incorporate a non-active control condition, such as a health education program, to isolate the effects of exercise intensity on sleep. Thirdly, while the MICT and HIIT groups were matched for total work output, the duration of exercise differed between the MICT, HIIT, and STRETCH groups, which may have influenced sleep quality as well. Finally, because sleep quality was not the primary outcome for the original intervention, there were too few good sleepers to examine the effect of the exercise intervention. While poor sleepers are the target group for treatment, future studies should aim to include a larger sample size of both poor and good sleepers for a full comparison.

Overall, the findings from this study suggest that both MICT and stretching may be more effective than HIIT for improving sleep in older adults with poor sleep quality. Critically, this is the first study to investigate the impact of HIIT vs. MICT on sleep in older adults. These results help inform an optimal exercise prescription for improving sleep quality to help keep older adults healthier longer.

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 Hamilton Integrated Research Ethics Board, McMaster University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AB and JJH: data analysis, manuscript writing. AK: data collection, manuscript editing. TK: data analysis, manuscript editing. All authors contributed to the article and approved the submitted version.

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Stress, Professional Lifestyle, and Telomere Biology in Elite Athletes: A Growing Trend in Psychophysiology of Sport

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Professional lifestyle and championship period often put a great deal of pressure on athletes, who usually experience highly stressful periods during training for competitions. Recently, biomarkers of cellular aging, telomere length (TL) and telomerase activity (TA), have been considered to investigate the effects of stress and lifestyle factors. Studies in non-athletic populations have shown that stress and poor lifestyle decrease TL and TA. On the other hand, it has been shown that in general, exercise increases TL and its activity, although the underlying mechanisms remained largely unexplored. TL and TA outcomes in elite athletes remain inconclusive and mainly affected by confounding factors, such as age. Elite athletes, therefore, might offer a unique target group for studying exercise-telomere hypothesis for further investigation of the roles of stressors on telomere-related biomarkers. In this perspective, we highlight the potentials for studying these psychophysiological markers in elite athletes in order to understand stress-aging relationship and potential underlying mechanisms. Moreover, we present important methodological aspects that could help in the development of future experimental designs.

Keywords: telomere, telomerase, competition, stress, elite athletes

INTRODUCTION

High demand training plans, following precise dietary programs, and attending a large number of competitions, often pressurize athletes, both physically and mentally. Stress is an inevitable factor and a common feature in competitive sports events, and there is no doubt that elite athletes undergo higher demands and are required to overcome these challenges for a successful preparation, performance, and competition (Campbell et al., 2018). Even though coaches and trainers try to adjust the athletes' training loads, intensive plans for engagement of athletes in training programs are documented in the literature (Pope et al., 2018). For instance, some athletes undergo 15–20 h of intensified training per week for years, which often results in an inadequate recovery time. Recovery is, however, highly important to diminish the risk of injuries and "overtraining syndrome" in elite athletes (Ehrlenspiel and Strahler, 2012). Overloading and overtraining can consequently cause long term and damaging physiological (e.g., decreased the testosterone/cortisol ratio) and psychological (e.g., burnout) effects (Freitas et al., 2014).

Several types of stress have been identified that play a role in overloading elite athletes prior to, during, and after competitions. Those include mental, physical, and technical demands for adequate preparation before competitions, such as demanding training environments, stressful coaching attitude, family stresses, imbalance between sport and non-sport lifestyle, and unrealistic commitments or expectations (Hanton et al., 2005). During or after competitions, other stressors play similar roles, such as rivalry, satisfying the expectations (e.g., media, fan, professional organizations, e.g., better ranking, or dealing with a diverse range of consequences following a non-successful competition) (Wilding, 2014). Collectively, various stressors exist and hence it is important to identify and apply strategies for minimizing or coping with those, which are highly individualized, mainly depending on personal capacity and available resources to each elite athlete. Acute stress and overcoming those seem feasible in many cases; however, chronic stress is often challenging to deal with and can cause long-term psychological and physical damages (Mariotti, 2015; Sabato et al., 2016). Some athletes, for instance, might not be able to apply adaptive coping strategies, which may mitigate the impacts of an innately stressful environment, and those are at higher risks for developing tissue injury and mental disorders, such as depression and anxiety (Purcell et al., 2019). These reactions are often due to activation of other cascades following the chronic activation of systems contributed in the stress response. For instance, overproduction of hormones, may lead to impaired metabolism and immune system that consequently influence overall well-being, performance and behavior of athletes (Lovallo and Buchanan, 2017). Several longitudinal investigations have shown that anxiety and stress as well as poor lifestyle are among important risk factors for a number of physical conditions, including diabetes, coronary heart disease, neurodegenerative, and autoimmune disorders, along with an increase rate of cancer and mortality (Seib et al., 2014). However, epidemiological studies and systematic reviews reported that elite athletes appear with more longevity and slightly lower mortality rate (with standard mortality ratio) compared with the general population (Kettunen et al., 2015; Lemez and Baker, 2015; Antero et al., 2020). In addition, physical fitness in elite athletes has been related to lower risks of somatic diseases (Teramoto and Bungum, 2010).

Accumulating evidence from the past decade suggests that one of the pathways through which stress may impact health is through accelerated cell aging as indexed by the length of the telomeric DNA at the end of chromosomes (Puterman et al., 2010). As a result, telomere length (TL) has emerged as a widely recognized biomarker of biological age. Short TL has been linked to a range of health problems, poor lifestyle, and early mortality (Epel et al., 2006). In this regard, the literature presents that there is a link between stress and shorter TL. Although no studies have yet identified potential moderators of this relationship, several studies have examined health behaviors as potential mediators through which stress affects health (O'Donovan et al., 2012; Shalev et al., 2013). This field has also captured high attention among sport scientists. The scientific literature suggests that a specific health behavior, such as physical activity, can moderate the impact of stress on cell aging (Puterman et al., 2018). Recent studies demonstrate that maintenance of a physically active lifestyle is related to longer TL. It is hypothesized that one mechanism of exercise-associated telomere lengthening is through increased levels of telomerase activity (TA) (Puterman et al., 2018). However, other potential mechanisms have also been proposed to describe how exercise may affect TL, including inflammation, oxidative stress, and proliferation or differentiation of satellite cells (Arsenis et al., 2017). Moreover, it has been made clear that elite athletes have longer TL than inactive and non-elite athletes (Abrahin et al., 2019). Although conflicting outcome exists in the literature (Rae et al., 2010), it also remains unclear whether and how the professional lifestyle of elite athletes and the competition-induced stress and anxiety or intensive training would affect cellular aging. Therefore, we emphasize on the potentials for studying these biomarkers in elite athletes in order to understand stress-aging relationship and underlying mechanisms. In this perspective, we first briefly explain the telomere biology and its relation to stress. Second, we review the relationship between mental disorders, psychological variables, lifestyle factors, interventions, and telomere/telomerase dynamics. Finally, we propose an overview from the dynamics of telomere and telomerase in elite athletes and methodological considerations in the measurement of TL and TA.

BIOLOGY OF TELOMERE AND EFFECTIVE FACTORS

Functions of Telomere/Telomerase

A telomere is a region at each end of a chromosome that protects the DNA. TL appears to be a marker of physiological age and it is related to several age-related diseases, lifespan, cancer, and lifestyle factors (Jylhävä et al., 2017). Human telomeres consist of tandem 5'-TTAGGG-3' repeats, and they form a loop-like structure; therefore, the very end regions of telomeres are concealed, and the end of chromosomes would not be identified as double-strand breaks (Blackburn, 2010). Upon shortening a telomere to a crucial length, the loop structures would not be able to be formed. Hence, the resulting telomere would be recognized as a nick in double-strand DNA, through the activation of DNA damage responses, resulting in the induction of cellular aging and programmed cell death (Pickett and Reddel, 2012). Dysfunction of telomeres may also lead to end-to-end fusions or end-degradation, causing genomic instability. Cellular aging and programmed cell death are thought to participate in the process of aging in normal cells, while genomic instability is considered a sign of cancer (Maciejowski and de Lange, 2017). In healthy somatic cells, TL represents a "mitotic clock" that is able to regulate how many divisions a particular cell can undergo. At least two primary mechanisms have been proposed by which the shortening process of telomeres could occur.

First, the replication of telomeres possesses a natural "end-replication problem," during cell division. In other words, the DNA sequences located at the edge of the linear chromosomes are not capable of being entirely replicated by DNA replication machinery. Second, it has been observed that the process of oxidative stress, caused by the overproduction of reactive oxygen species, can explicitly cause breaks at 5'-TTAGGG-3' repeats, leading to the shortening of the TL (Baird, 2008).

Human telomerase constitutes two significant subunits, a catalytic enzyme human telomerase reverse transcriptase (hTERT) and an RNA template (hTR or hTERC). The telomerase enzyme employs its RNA template for synthesizing TTAGGG sequences to resolve the obstacle of telomere shortening. In addition to the classic function of telomere lengthening, the telomerase enzyme has several other duties that are independent of the TL (so-called extra-telomere activity), such as increasing stress-resistance, cell survival, protection of mitochondrial functions, mediating DNA damage response, inhibition of apoptosis, and promoting neuroprotective signaling (Cong and Shay, 2008). These properties are essential for the anti-aging process. The TA is controlled by post-translational modifications of the hTERT protein, including phosphorylation and nuclear translocation as well as transcriptional control of hTERT (Wojtyla et al., 2011). More precisely, experiments have demonstrated that alterations in the TA might occur within minutes to a few hours following the exposure to specific molecular stimuli, such as inflammatory cytokines, stress hormones, and growth factors leading to post-translational modifications of the hTERT protein (de Punder et al., 2019).

Stress and Telomere Biology

Acute stress response is regularly referred to as a spectrum of affective, cognitive, behavioral, and physiological responses to specific stressors, formed by basal physiological circumstances and cognitive biases (Epel et al., 2018). The response of this multi-system may include anticipatory arousal prior to a stressful situation, peak reactivity during an event, and recovery to baseline following a stressful event. Inappropriate response to acute stress may result in detrimental changes in telomere regulation. For instance, autonomic over-reactivity has been correlated with decreased immune cell function, as well as increased cortisol reactivity to stressors with shorter length of telomeres within the immune cells (Jiang et al., 2019). Perseverative cognition, e.g., rumination and worriness, are capable of exacerbating the increased physiological reactivity and delayed recovery, and it may serve as internal stressors. Notably, shorter TL has also been associated with perseverative cognition, such as negative mind wandering and more importantly, anticipatory threat appraisals to acute stressors (Conklin et al., 2019).

The profile of acute stress reactivity is mainly affected by allostatic cases, such as basal levels of neuroendocrine and autonomic activity, inflammation, and metabolic hormones. Prolonged reactivity and chronic exposure to a particular stressor may lead to disturbed allostatic states, followed by pernicious health consequences (Goldstein and McEwen, 2002). The regulation of telomeres seems to be involved in this condition, as a lower TA and shorter TL have been linked to the decreased vagal tone, increased basal levels of cortisol, oxidative stress, and inflammation (Conklin et al., 2019).

Collectively, these investigations propose that chronic stress expedites the process of cellular aging (Epel et al., 2004). Several mechanisms underlying the relationship between telomere dynamics and stress have been characterized (Epel et al., 2009). One of such facets is the impaired allostatic load model that proposes the stress can affect the control of the HPA axis, thereby boosting the secretion of cortisol, participating in allostatic load, and in turn dysregulating telomere maintenance. Indeed, in humans, shorter TL is correlated with higher cortisol reactivity, and *in vitro* evidence shows that increased glucocorticoid concentrations are linked with diminished TA (Jiang et al., 2019). Although, some studies have suggested that the testosterone levels were positively associated with TL (Drury et al., 2014); hence, remained the field with contradictory results (especially in TA).

Nonetheless, it is necessary to perceive that under acute stress conditions, circulating immune cells would be depleted. Thus, a compensatory increase occurs to replace the eliminated cells with young ones, resulting in the longer TL determination and higher TA. Alternatively, chronic stress leads to the induction of continued replication stress and in turn, stimulates telomere attrition and reduces TA. This phenomenon explains the "telomerase paradox": under acute stress conditions, telomerase would be more activated to protect telomeres; while in chronic stress, as observed in depressed individuals, the activity may be lower, leading to progressive telomere dysfunction (Epel, 2012). A stress triad about the maintenance of telomere has been suggested elsewhere (Epel and Prather, 2018). Basically, chronic exposure to stressors leads to continuously higher perceived stress and subsequent stress arousal, which in turn remarkably influence telomere attrition (Mathur et al., 2016). Other reports propose that inflammation plays a crucial role in telomere attrition and that continued stress is associated with the shorter TL and low-grade inflammation compared with healthy conditions without the presence of any inflammation (Squassina et al., 2019).

Mental Disorders, Psychological Variables, and Telomere/Telomerase Dynamics

In relation to mental disorders, shortened TL and decreased TA have been associated with mood disorders (such as depression and bipolar disorder), schizophrenia and other psychotic disorders, obsessive-compulsive disorder, anxiety disorders (such as post-traumatic stress disorder, panic disorder, social phobia, and generalized anxiety disorder), and psychoactive substance use (see for review, Deng et al., 2016; Boccardi and Boccardi, 2019). It is noteworthy that robust preclinical and clinical evidence suggests that psychotropic medication (e.g., antidepressants) may exert a positive effect on TL and TA in psychiatric disorders (Zhou et al., 2011). In addition, we identified the literature pointing to some psychosocial variables, including higher perceived stress, distress, defensiveness, anxiety scores and poor mental health, socioeconomic status, and social support that have been correlated to the shortened TL and decreased TA (Starkweather et al., 2014). It has been made clear that the positive dispositions characteristics such as optimism, emotional intelligence, and trait mindfulness as well as problem-focused coping styles were associated with longer TL (Schutte et al., 2016; Archer, 2017).

Lifestyle and Telomere/Telomerase Dynamics

Studies have examined TL and TA in various lifestyle contexts. Our literature review revealed that physical exercise might have a positive effect on TA and TL. Several animal models and experiments in clinical and non-clinical settings on humans have been carried out to study the effect of physical exercise on the TA and TL (Deng et al., 2016; Stellos and Spyridopoulos, 2019). While some systematic reviews (Mundstock et al., 2015; Lin X. et al., 2019) have demonstrated beneficial effects of physical activity on TL and TA, mainly with moderate level of exercise compared with low or intense exercise, other systematic reviews (Ludlow et al., 2013; Arsenis et al., 2017) could not conclude if a relationship exists between physical activity and TL and TA. In particular, it is still debated whether exercise can directly impact TL. Notwithstanding, some studies highlighted that high exercise load has been related to a decrease in the TL and an increase in TA (Bruunsgaard et al., 1999). In this regard, de Carvalho Cunha et al. (2018) showed that more vigorous exercise with above lactate threshold could also decrease the expression of proteins related to telomere protection (p53 activity and sheltering proteins). Moreover, a new animal experiment has shown that high intensity interval training with short- and long-term intervals does not change the TA (Sadeghi-Tabas et al., 2020). Though there are some important methodological shortcomings (e.g., patterns specific to cell-type or genotype, heterogeneity of studies, small sample size, blinding of researchers, etc.) in relation to load of exercise and telomere biology. Researchers have suggested that more effort is required to mechanistically examine the impact of various modalities of exercise on TL and TA, and future studies need to questions about design of exercise modalities, not only exercise type, but also the intensity, method, or type of stimuli (Jiménez-Pavón et al., 2019).

Several studies have also assessed the impact of diet on TL and TA, and suggest that low-calorie restriction, prolonged fasting, and overeating decrease both TL and TA (Deng et al., 2016). Consumption of meals high in fiber and vitamins (both dietary and supplemental) is related to telomere regulation (higher TL), whereas eating processed meats and foods high in polyunsaturated fats is related to shorter TL. In a multiethnic study, researchers have identified that higher intake of processed meat is significantly associated with shorter TL (Nettleton et al., 2008). The role of sleep in telomere/telomerase dynamics has been described well. Previous studies reported that poor sleep quality and sleep less than 6 h per night have been correlated with shorter TL and lower TA (Shalev et al., 2013). Moreover, excessive alcohol consumption, and cigarette smoking and tobacco consumption have also been associated with shorter TL and TA (Weischer et al., 2014). Collectively, these findings

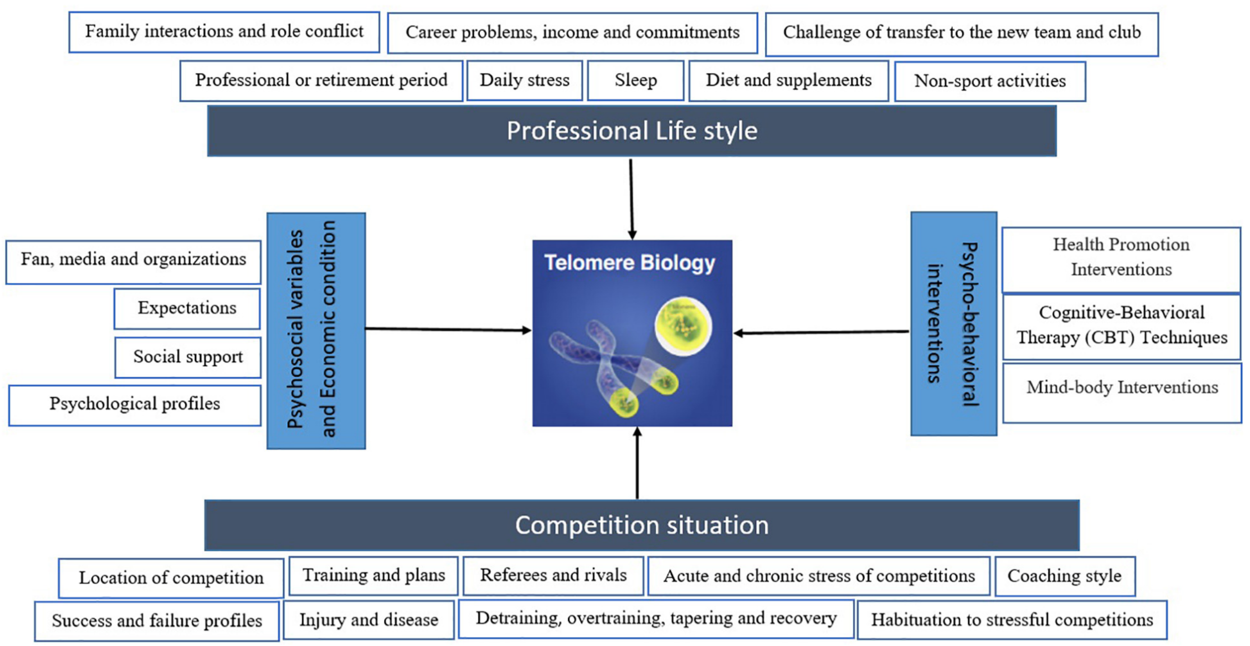

FIGURE 1 | A schematic model depicting competition and its effective factors as well as professional lifestyle that may effect on telomere biology in elite athletes. Moreover, psychosocial variables and economic condition can alter telomere length (TL) and telomerase activity (TA). Additionally, there are multiple psycho-behavioral intervention that may result in the TL and TA changes, including increases in intracellular TA and lengthening of telomeres. The biological mechanisms must be considered to outline a map of a more complete model.

present that diet and lifestyle, and habits can markedly influence both TL and TA. Since athletes follow a special diet or follow specific life styles, it is important to consider when investigating TL and TA in this population compared with non-athlete matched individuals.

Psycho-Behavioral Interventions and Telomere/Telomerase Dynamics

It is important to note that some lifestyle and psycho-behavioral interventions, including mindfulness, yoga, qigong practice intervention, cognitive behavioral trophies interventions, and meditation could influence TL and TA under healthy and pathological conditions (Schutte and Malouff, 2014; Deng et al., 2016; Conklin et al., 2019). A pioneering study on the effect of an integrative health promotion intervention, including low-calories foods, moderate aerobic exercise, psycho-behavioral practice, and group support session, has observed that TA increased significantly after the 3-month intervention where it was also significantly correlated with decreases in psychological distress (Ornish et al., 2013). In this regard, it is still not clear which interventions might produce the optimal effect on TL and TA.

Telomere/Telomerase Dynamics in Elite Athletes

Investigations on telomere/telomerase dynamics in elite athletes are limited; however, a growing body of empirical research has shown that young elite athletes have longer TL compared with their inactive peers (Muniesa et al., 2017). Moreover, a group of researchers reported that the whole blood leukocyte telomeres were longer in elite endurance athletes compared with healthy controls (Sousa et al., 2020). In addition, Simoes et al. (2017) indicated that elite sprinters had longer TL, lower body fat and BMI, and a better lipid profile than age-matched controls. Noteworthy, a study in eight professional marathon runners indicated that TA in peripheral blood leukocytes before and after running seven marathons in 7 days did not significantly differ, demonstrating that the impact of physical activity on TA may become saturated in individuals involved in elite endurance athletic activities (Laye et al., 2012). On the other hand, Werner et al. (2009) have demonstrated that in peripheral blood leukocytes, isolated from professional endurance athletes TA, expression of telomere-stabilizing proteins, and downregulation of cell-cycle inhibitors have been increased compared with untrained individuals. A new meta-analysis has concluded that high level chronic physical training (aerobic and resistance training) may provide protective effects on TL (Abrahin et al., 2019). However, one needs to consider the influence of variables in a diverse range of studies that can alter the outcome of TL. For example, elite athletes are motivated to choose difficult lifestyles and frequent delivery of stress in the competition and the championship period that cause a higher risk of injury or illness. This in turn may negatively impact their health and faster aging in some periods or overall in the life span (Tanaka and Seals, 2008). If this hypothesis turns out to be correct, lifestyle associated with their needs for rigorous training-competition and dietary requirements could be chosen in such a way to modulate markers of chronic inflammation and redox balance, to yield a healthier functional aging and athletic performance (Mikkelsen et al., 2013).

METHODOLOGICAL CONSIDERATIONS FOR TL AND TA MEASUREMENT

With a growing research interest in telomere biology, a consensus in laboratory measurements seems critical with high precision and accuracy. Currently, the TL and TA are measured in many different laboratories utilizing different assays (e.g., telomere restriction fragment, length analysis by Southern blot analysis, quantitative PCR, and Telomerase Repeat Amplification Protocol) (Epel et al., 2010; Lin J. et al., 2019). Application of different approaches makes it challenging to compare results from different studies.

Based on tissue type and collection methods (e.g., blood including plasma, serum and peripheral blood mononuclear cells and saliva samples, including swabs and buccal cells), several specimen types have been used for TL and TA measurement (Lin J. et al., 2019). Each specimen offers advantages and challenges and, due to cell type differences, it might influence TL and TA outcomes. For instance, quantitative-PCR provides the advantage of being able to use smaller amounts of DNA, thereby making it amenable to epidemiology studies involving large numbers of people. An alternative method uses fluorescent probes to quantify not only mean TL, but also chromosome-specific TL. Of note, all these novel techniques for TA measurement are currently at the proof of concept stage, and only a number of those have been applied in studies involving clinical tissues or body fluid samples. When incorporating TL and TA into a research study, it is important to thoroughly evaluate the research question, population, sample type, timing of the analysis, and available resources in order to select optimal TL and TA measurement method.

To our knowledge, no study has evaluated TA and TL in elite athletes within the sport context, such as competition (prior, during and after). In future studies, measuring TA and TL biomarkers in this population may require extra attention in methodology with a rigorous design to accommodate specificity and characteristics of this population.

CONCLUSION AND FUTURE DIRECTIONS

In general, studies in different populations have shown that lifestyle together with acute and chronic stress affect cellular aging. Psychological disorders, interventions, physical activity, diet, sleep, alcohol consumption, and smoking may alter cellular aging differently and through a diverse range of mechanisms that are currently under investigation. Target population is important in this context and elite athletes have been less studied, while this population can offer a unique population for studying biomarkers of aging, including TL and TA. Few studies are available in elite athletes, but those have mainly focused on physiological aspects, and a lack is evident in relation to psychological and lifestyle factors influencing TL, and TA in this population. **Figure 1** depicts a simplified overview of potential parameters and aspects that can influence telomere biology in athletes, within sport science and athletic competitions.

Moreover, psychosocial variables and economic condition can alter TL and TA. Additionally, there are multiple psycho-behavioral interventions that may result in the TL and TA changes, including increases in intracellular TA and lengthening of telomeres. The biological mechanisms must be considered to outline a map of a more complete model.

There are a number of open questions that investigators are encouraged to pay attention to for the future studies in this regard. One of the critical points is to consider the level of competition (e.g., long-term league as a chronic stress and tournaments as well as playoff matches as acute stress) and the level of competitive stress on the dynamics of telomere/telomerase. For instance, the greater importance of competition (e.g., final and pre-final competitions) causes more drastic changes in the level of salivary stress markers (Chennaoui et al., 2016). On the other hand, long-term league may suppress immunity function and increase the risk of physical injury in elite athletes (Papacosta et al., 2013).

Psychological variables (e.g., perceived stress, stress reactivity, trait anxiety, coping, etc.) potentially influencing telomere/telomerase are not well investigated either. Since these variables have been well-documented in non-sport literature, and populations with psychological disorders and healthy individuals, can also inspire elite sport studies in the future. Considering that a few elite athletes may also have a range of psychological disorders (Purcell et al., 2019), this sub-population might also offer a platform for investigation of psychological factors. On this line, the International Olympic Committee has focused on the identification, diagnosis, signs, and symptoms, as well as the treatment of these disorders. Studies have demonstrated that psychological interventions, such as meditation and mindfulness, are capable of increasing the TL and TA in clinical populations and patients (Schutte and Malouff, 2014). Future interventions in the field of competitive stress can examine this hypothesis. Stress prevention, management techniques, and changing the stress mindset of elite athletes (even in the adolescence when they are deciding to dedicate their life to be professional), as well as offering sport psychology services to elite athletes for better management of competitive stress and life interactions can be a new perspective in telomere biology in professional athletes.

The type sport and competition, competition season periodization, and intensity of exercise, along with considering gender and age, can increase the generalizability of future studies. In this regard, recent reviews and observational experiences (Ehrlenspiel and Strahler, 2012; Slimani et al., 2017; van Paridon et al., 2017) have indicated that some variables are associated with the psychophysiological changes to competition in elite athletes (e.g., challenge of transfer to the new team and club, location of competition, habituation to stressful competitions, poor sleep, referee and rivals, gender, type of sport, social interaction with fans, media and organizations, warm-up and preparing for competition, coaching styles, social support, expectations, preparation levels, success and failure profiles, commitments and plans, etc.). Each of these variables is worth investigating in the field of telomere biology in future studies. Some of the essential questions that need to be investigated are related to detraining, overtraining, tapering, and recovery periods in elite athletes. Moreover, it is not yet clear if training and exercise might be highly effective to overcome TL shortening and this makes the complex puzzle of mechanisms a subject for further investigation.

The effects of doping and even placebo effects of doping on these cellular aging markers are still opaque. On this subject, an animal model has been reported, in which Stanozolol (a performance-enhancing anabolic androgenic steroid) could induce TA in the liver tissue of rats and exercise reversed this induction, reflecting possible premature aging in the liver tissue (Ozcagli et al., 2018). This area could be a hot topic for future research and provide recommendations to the World Anti-Doping Agency. Physical injuries are one of the areas of interest in telomere biology. It has been made clear that the relative TL in patients (anterior cruciate ligament rupture) with non-contact sports was greater than those with contact sports (Daechavijit et al., 2019). Furthermore, injuries and psychological indices associated with a sports injury, for example, injury, anxiety, and returning to competition after the injury, can open a new horizon in this field.

Scientific research has unraveled the impact of lifestyle and its influencing factors, such as daily stress, family interaction, sleep parameters, diet, physical activity, and smoking on telomere/telomerase dynamics in different populations (Weischer et al., 2014; Deng et al., 2016). Future studies should provide the opportunity to study the lifestyle indicators in elite athletes. For instance, an elite athlete may practice long hours along with external non-sport activities and education, and be subject to overtraining and burnout. Interactions within the family (e.g., spouse) and parents can also be effective indicators. Moreover, the retirement period of elite athletes can offer a potential for studying aging of this population compared with non-competitor athletes. Investigations have estimated that the retirement period (especially in involuntary retirement) and end of athletic career steps sometimes accompanied by sickness, role conflict, loneliness, economic damage, addiction, reduced social support, and depression (Wylleman et al., 2015; Mannes et al., 2019). Looking at potential interventions (e.g., regular exercise and psychology-medical services) in retirement period can be helpful for addressing potential mechanisms of TL and TA.

Since blood sampling and complicated measurement techniques might be challenging during a competitive situation, non-invasive methods, for example, obtaining salivary samples, would be beneficial. Some recommendations have been created (Lin J. et al., 2019) that are continually being updated. In addition, to find the mechanisms of TL and TA changes, investigation of intracellular cascades (not only *in vivo* but also *in vitro*) must be considered.

Taken together, in the context of elite athletes involved in highly competitive sports, several psychological, neurological, hormonal, immunological, oxidative, and cellular responses play roles in aging that are not yet thoroughly investigated. The longitudinal studies are warranted to investigate the possible underlying mechanisms of the effects of lifestyle, competition-induced stress, and athletes' championships period on cellular markers of aging to identify if a particular dynamic affects TL and TA in this population. This would in turn result in identification of modifiable factors, such as lifestyle changes, or dietary recommendations for elite athletes to experience a healthier life and aging.

AUTHOR CONTRIBUTIONS

All the authors discussed the hypothesis and the manuscript content, wrote the first draft, and read and approved the final manuscript.

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ORIGINAL RESEARCH
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Neurophysiological Differences Between Women With Fibromyalgia and Healthy Controls During Dual Task: A Pilot Study

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Background: Women with FM have a reduced ability to perform two simultaneous tasks. However, the impact of dual task (DT) on the neurophysiological response of women with FM has not been studied.

Objective: To explore both the neurophysiological response and physical performance of women with FM and healthy controls while performing a DT (motor–cognitive).

Design: Cross-sectional study.

Methods: A total of 17 women with FM and 19 age- and sex-matched healthy controls (1:1 ratio) were recruited. The electroencephalographic (EEG) activity was recorded while participants performed two simultaneous tasks: a motor (30 seconds arm-curl test) and a cognitive (remembering three unrelated words). Theta (4–7 Hz), alpha (8–12 Hz), and beta (13–30) frequency bands were analyzed by using EEGLAB.

Results: Significant differences were obtained in the healthy control group between single task (ST) and DT in the theta, alpha, and beta frequency bands (p-value < 0.05). Neurophysiological differences between ST and DT were not found in women with FM. In addition, between-group differences were found in the alpha and beta frequency bands between healthy and FM groups, with lower values of beta and alpha in the FM group. Therefore, significant group*condition interactions were detected in the alpha and beta frequency bands. Regarding physical condition performance, between groups, analyses showed that women with FM obtained significantly worse results in the arm curl test than healthy controls, in both ST and DT.

Conclusion: Women with FM showed the same electrical brain activity pattern during ST and DT conditions, whereas healthy controls seem to adapt their brain activity to task commitment. This is the first study that investigates the neurophysiological response of women with FM while simultaneously performing a motor and a cognitive task.

Keywords: dual task, pain, physical fitness, EEG, strength

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INTRODUCTION

Fibromyalgia (FM) is characterized by chronic, widespread, and persistent pain and its prevalence is around 2% to 3% worldwide (Helmick et al., 2008). Nevertheless, FM is accompanied by other symptoms, such as stiffness, mobility problems, sleep disorders, anxiety, depression, or cognitive impairments (Wolfe et al., 2010). The study of cognition and FM is a growing field of research since previous studies have reported cognitive impairments in several domains of people with FM, including long-term memory (Canovas et al., 2009), short-term memory (Park et al., 2001), working memory (Coppieters et al., 2015), processing speed (Del Paso et al., 2015), or even an abnormal EEG signal at rest (Villafaina et al., 2019a,b).

Due to the impact of FM symptoms, people with FM showed a diminished quality of life and reduced ability to perform activities of daily living (Burckhardt et al., 1993; Huijnen et al., 2015). In this regard, activities of daily living are commonly presented under the dual-task paradigm (where two or even more tasks are simultaneously required) (Yuan et al., 2015). People with FM have shown a diminished physical performance when two tasks are simultaneously presented during postural control (de Gier et al., 2003), balance (Villafaina et al., 2019c) or when compared with healthy controls in physical fitness tests (Villafaina et al., 2018, 2019d).

Progress in mobile and wireless technologies have allowed studying the impact of DT on the electroencephalography (EEG) (Wagner et al., 2012; Winslow et al., 2016) during ecological scenarios. In this regard, previous studies have explored brain dynamics during dual-task conditions in young and older people (De Sanctis et al., 2014; Malcolm et al., 2015; Bogost et al., 2016). However, the impact of DT on neurophysiological measures has not been investigated. Therefore, the present study aimed to explore the neurophysiological response of women with FM and healthy controls while performing a DT (motor–cognitive). We hypothesized that DT would engage brain areas related to executive function (prefrontal cortex) (Ford et al., 2002; Giraud et al., 2007) and areas related to sensorimotor integration (sensorimotor cortex and posterior parietal cortex) (Sipp et al., 2013; Beurskens et al., 2016; Bradford et al., 2016). Moreover, neurophysiological differences between healthy controls and people with FM could emerge since people with FM reported an attention deficit disorder (van Rensburg et al., 2018; Yilmaz and Tamam, 2018). This is because people with FM have impaired the ability to perform two simultaneous tasks (Huijnen et al., 2015; Villafaina et al., 2018, 2019d).

MATERIALS AND METHODS

Participants

Twenty-five women with fibromyalgia participated in this study with a cross-sectional design. They were divided into two groups: (1) women with fibromyalgia (N = 17; age = 51.88 [7.30]) and (2) age- and gender-matched healthy controls (N = 19; age = 50.95 [6.83]) (**Table 1**). The Extremadura Association of Fibromyalgia (Spain) recruited the women with FM by telephone calls in April 2018.

TABLE 1 | Participants' characteristics.

Measurements	Women with FM Mean (SD)	Healthy controls Mean (SD)	*p*-value
Sample size (*N*)	17	19	
Age (years)	51.88 (7.30)	50.95 (6.83)	0.975
BMI (kg/m^2)	27.54 (4.69)	24.07 (3.89)	0.029
Fat mass (%)	26.77 (7.85)	19.34 (7.33)	0.010
VAS for pain (0–100)	63.53 (16.18)	–	–
FIQ total score	53.31 (10.29)	–	–

BMI, body mass index; FIQ, fibromyalgia impact questionnaire; VAS, Visual Analog Scale.

The inclusion criteria for participants were as follows: (a) be a female and aged between 30 and 75 years, (b) be able to communicate with technicians, and (c) have read and signed the written informed consent. In addition, women with FM have to be diagnosed by a rheumatologist, according to the American College of Rheumatology's criteria (Wolfe et al., 2010). However, the following exclusion criteria were defined as follows: (a) had contraindications for physical activity, (b) have been suffering from a psychiatric or neurological diagnoses according to their current medical history, and (c) were pregnant. Moreover, healthy controls were excluded if they suffered from any pain that lasted for more than three months in the last six months.

The University of Extremadura bioethical research committee approved the procedures (approval number: 62/2017), following the updated Declaration of Helsinki. All the participants read and signed the informed consent prior to the first assessment.

Procedure

The body composition measurement was measured using the using the Tanita Body Composition Analyzer BC-418 MA. Moreover, the impact of the disease was evaluated with the (Bennett, 2005; Esteve-Vives et al., 2007) Spanish version of the Fibromyalgia Impact Questionnaire (FIQ), which evaluates the impact of symptoms (in several domains such as pain, fatigue, rested, stiffness, anxiety, depression, physical impairment, feeling good, or work missed). Furthermore, the pain intensity was measured through the VAS for pain (0–100) (Boonstra et al., 2008; Hawker et al., 2011), referring to the day they were evaluated. Body composition was evaluated in both FM and healthy groups whereas the impact of the disease and pain intensity were assessed (through an interview) exclusively in the FM group.

EEG was recorded while participants performed the arm-curl test (Ariadna Aparicio et al., 2015). Therefore, participants have to be seated in a chair holding a 2.3-kg weight and encouraged to perform, as many times as possible for 30 s, arm curls (to lift the weight and return to the starting position) through a full range of motion. This physical fitness test was selected since it could potentially discriminate women with fibromyalgia from healthy women (Ariadna Aparicio et al., 2015) and the performance is associated with the severity of the symptoms

(Soriano-Maldonado et al., 2015). The best of the two trials, for each arm, was chosen for analyses purposed.

Participants performed the physical fitness test in both single-task (ST) and DT conditions. The simultaneous cognitive task consisted of remembering three random words. Therefore, participants were encouraged to think in these words while the arm-curl test was being performed. The cognitive performance and correct responses were registered. Conditions (ST and DT) were randomized.

Instrument and Measures

The EEG signal was record using the Enobio device (Neuroelectrics, Cambridge, MA, United States) (Ruffini et al., 2007). The EEG signal was recorded in a total of 19 scalp locations according to the International 10–20 system (Homan, 1988) in different brain areas such as frontal (Fz, Fp1, Fp2, F3, F4, F7, and F8), central (Cz, C3, and C4), temporal (T3, T4, T5, and T6), parietal (Pz, P3, and P4), and occipital (O1 and O2).

Two electrodes placed in each mastoid served as reference. Moreover, the impedance was kept below 5 KΩ and a sampling rate of 500 Hz was used. Preprocessing steps and data analyses were conducted with the EEGlab toolbox (MatLab) (Delorme and Makeig, 2004). A 1-Hz high-pass filter was used, and the line noise was removed using the CleanLine algorithm in EEGlab. In order to reject bad channels and correct continuous data, the Artifact Subspace Reconstruction (ASR) was used. In this regard, if a channel is correlated with the surrounding channels less than 0.8, the channel was rejected. Moreover, principal components (PCs) were classified into high variance (in this case, with a standard deviation of 8 from the calibration data) or normal variance. A window rejection criterion of 0.25 was set, meaning that if more than 0.25 of channels are judged to be bad even after ASR, the window will be rejected. Then, bad channels were interpolated and the data was re-referenced to average. In addition, the independent component analysis (ICA) was conducted (Jung et al., 2000) and single equivalent current dipoles estimated, looking for the symmetrically constrained bilateral dipoles. Dipoles located outside the brain were removed using the independent components (ICs) when the dipoles' residual variance was larger than 15%. Moreover, a visual inspection of dipoles located inside or outside the brain was performed. Lastly, the fast Fourier transform (FFT) method was used to compute spectral decomposition after splitting continuous data in 1-s epochs. Therefore, theta (4–7 Hz), alpha (8–12), and beta (13–30) power spectrums were computed.

Additionally, in order to report EEG sources analysis, evoke-related potentials (ERPs) were generated with a 7000-ms window time-locked, and dipoles were then estimated utilizing DIPFIT. Thus, a Kmeans cluster procedure (k = 10) was performed for clustering dipoles, using dipole location. Different clusters were performed according to the group and condition. Thus, for within- and between-group analysis purposes, clusters were obtained taking into account their group (fibromyalgia or healthy control) and condition (dual or single task). Therefore, ERSP were extracted to observe the amplitude and latency as well as the time–frequency analysis for source analyses. For analysis purposes, only clusters which contain the signal of the majority of the sample were selected. Results from these analyses are presented in **Supplementary File 1**.

Statistical Analysis

A 2 × 2 design using the EEGLAB study design was used to explore the EEG data during ST versus DT in both healthy and women with FM. Permutation statistics with 2000 repetitions and the false discovery rate (FDR) correction were applied for EEG analyses.

In addition, the SPSS statistical package (version 22.0; SPSS, Inc., Chicago, IL, United States) was used to analyze the arm-curl test performance in both ST and DT conditions. Moreover, non-parametric analyses were conducted taking into account the results of Shapiro–Wilk and Kolmogorov–Smirnov tests. Therefore, the Wilcoxon signed-rank test was used to assess differences within groups, whereas Mann–Whitney U or chi-squared tests (when appropriate) were used to explore between-group differences in both ST and DT conditions. Additionally, the dual-task cost (DTC), which measures the losses of performance due to motor–cognitive interference, was calculated as follows:

DTC = (Result of DT condition – Result of ST condition)/Result of ST condition.

Effect size [r] was calculated for each the ST and DT comparisons (Fritz et al., 2012). Values of 0.37, 0.24, and 0.10 represent large, medium, and small effect sizes, respectively (McGrath and Meyer, 2006). The alpha level of significance (0.05) was adjusted according to the Benjamini–Hochberg procedure to avoid type I error derived from multiple comparisons (Benjamini and Hochberg, 1995).

RESULTS

Impacts of Dual Task on Physical and Cognitive Performance

Table 2 shows within- and between-group differences. Regarding within group analyses, differences were not found in women with FM nor healthy controls (p-value > 0.05). Nevertheless, between groups, analyses showed that women with FM obtained significantly worse results in the arm curl test than healthy controls in both DT (p-value < 0.001) and ST (p-value < 0.001) conditions.

Table 3 shows the between-group differences in the arm-curl test DTC and cognitive performance (successful responses). Differences between healthy controls and women with FM were not observed in the DTC.

Impacts of Dual Task on EEG Frequency Bands

Figure 1 shows the theta power spectrum (4–7 Hz) topographic maps in the women with FM and healthy controls during ST and DT conditions. Differences (p-value < 0.05) were only observed in healthy controls when compared ST and DT conditions. Significant differences between groups (p-value < 0.005) were located in the frontal (Fz, F3, F4, F7, and F8), central

TABLE 2 | Within- and between-group comparisons in the arm-curl test during ST and DT in women with FM and healthy controls.

Arm-curl performance (rep)	ST Median (IQR)	DT Median (IQR)	*Z*	*p*-value	Effect size
Within-group comparisons					
Women with FM	17.00 (4.5)	15.50 (4.3)	−1.082	0.279	0.262
Healthy controls	23.50 (3.5)	23.00 (4.5)	−0.260	0.795	0.248
Between-group comparisons					
Z	−3.966	−4.488			
p-value	< 0.001	<0.001			
Effect size	−0.661	−0.748			

DT, dual task; DTC, dual-task cost; IQR, interquartile range; Rep, repetitions; ST, single task. p-value < 0.05.

TABLE 3 | Between-group comparisons in the dual-task cost and cognitive performance in the arm-curl test in women with FM and healthy controls.

Arm-curl performance (rep)	Women with FM Median (IQR)	Healthy controls Median (IQR)	*Z*	*p*-value	Effect size
Successful responses	3 (0)	3 (0)	–	0.615[a]	–
Dual-task cost	−0.04 (0.17)	0.04 (0.12)	−1.016	0.315[b]	0.170

DT, dual task; DTC, dual-task cost; IQR, interquartile range; Rep, repetitions; ST, single task. [a]p-value obtained from chi-squared test. [b]p-value obtained from Mann–Whitney U test. p-value < 0.05.

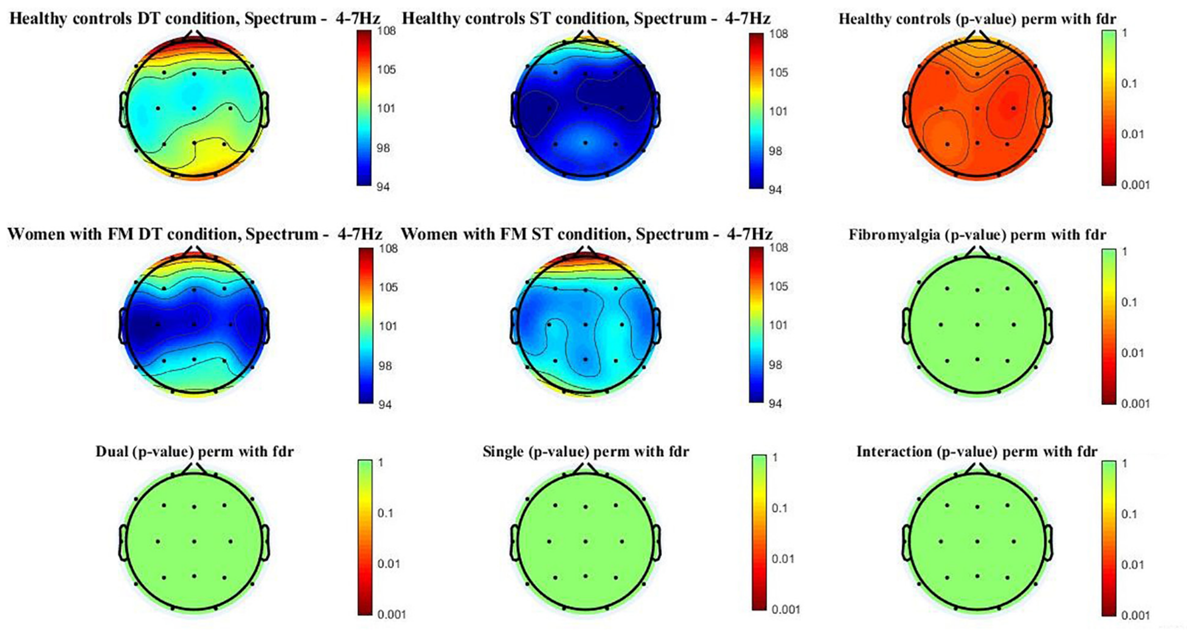

FIGURE 1 | Theta power spectrum (4–7 Hz) topographic maps in women with FM and healthy controls. Differences were only located ($p < 0.05$) between ST and DT conditions in healthy controls in the following scalp locations: frontal (Fz, F3, F4, F7, and F8), central (Cz, C3, and C4), temporal (T3, T4, T5, and T6), parietal (Pz, P3, and P4), and occipital (O1 and O2).

(Cz, C3, and C4), temporal (T3, T4, T5, and T6), parietal (Pz, P3, and P4), and occipital (O1 and O2). Higher theta power spectrum values were found in the DT compared to ST values. However, significant between-group differences or group*condition interactions were not found.

Figure 2 shows the alpha power spectrum (8–12 Hz) topographic maps in the women with FM and healthy controls during ST and DT conditions. Differences (p-value < 0.05) were observed in healthy control when compared ST and DT conditions [scalp locations: frontal (Fz, Fp1, Fp2, F3, F4, F7, and F8), central (Cz, C3, and C4), temporal (T3, T4, T5, and T6), parietal (Pz, P3, and P4), and occipital (O1 and O2)]. Moreover, significant between-group differences (p-value < 0.005) were found when comparing healthy controls and women with FM in the DT condition [scalp locations: frontal (F7), central (Cz, C3, and C4), temporal (T3, T5, and T6), parietal (Pz and P4), and occipital (O2)]. The group*condition interactions were also significant in the frontal (Fp1, F4, F7, and F8), central (Cz, C3, and C4), temporal (T3, T5, and T6), and occipital (O1).

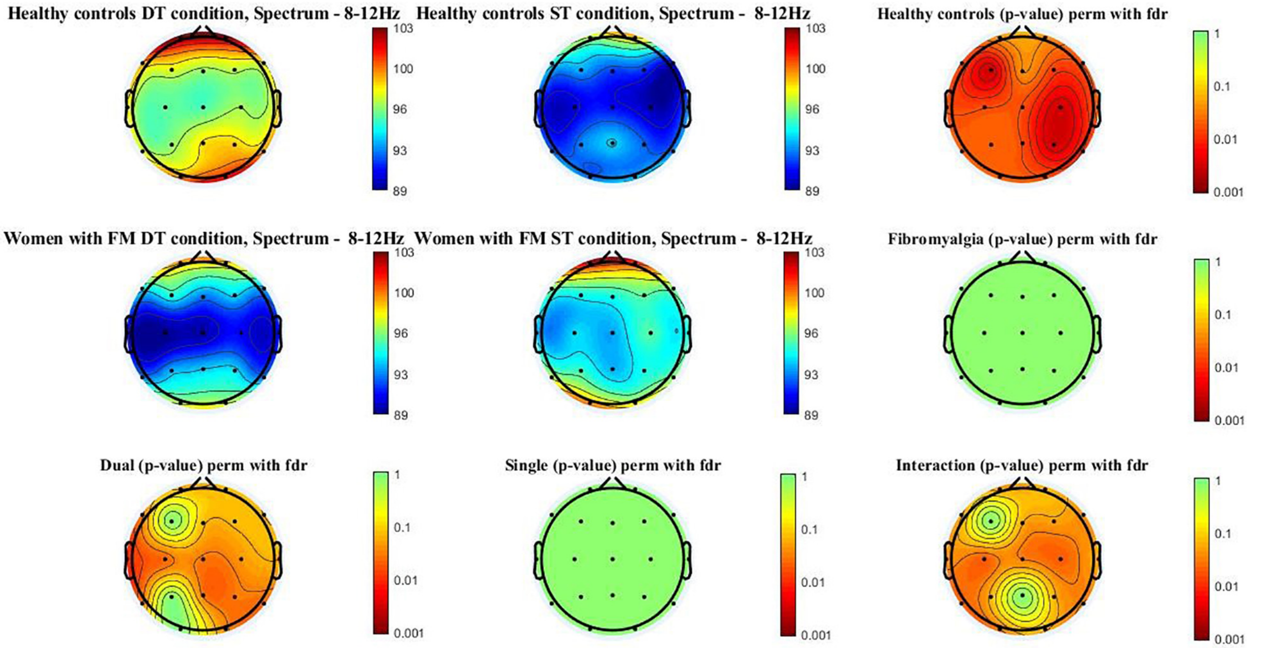

FIGURE 2 | Alpha power spectrum (8–12 Hz) topographic maps in women with FM and healthy controls. Differences were only located ($p < 0.05$) between ST and DT conditions in healthy controls and between healthy controls and women with FM in the DT condition. In addition, the interactions group*condition is significant in the following scalp locations: central (Cz, C3, and C4), temporal (T5 and T6), and occipital (O1).

Figure 3 shows the beta power spectrum (13–30 Hz) topographic maps in the women with FM and healthy controls during ST and DT conditions. Differences (p-value < 0.05) were observed in healthy control when comparing ST and DT conditions [scalp locations: frontal (Fz, Fp1, Fp2, F3, F4, F7, and F8), central (Cz, C3, and C4), temporal (T3, T4, T5, and T6), parietal (Pz, P3, and P4), and occipital (O1 and O2)]. Moreover, significant between-group differences (p-value < 0.005) were found when comparing healthy controls and women with FM in the DT condition [scalp locations: frontal (F7, F8, Fp1, and Fp2), central (Cz, C3, and C4), temporal (T3, T4, T5, and T6), parietal (Pz and P4), and occipital (O2)]. The group*condition interactions were also significant in the frontal (Fp1, Fp2, Fz, F4, F7, and F8), central (Cz, C3, and C4), temporal (T3, T4, T5, and T6), parietal (P3 and P4), and occipital (O1).

Source Analyses

Supplementary File 1 shows the results of the complementary ERSP sources analyses. Differences within-group (ST vs. DT) were found in both healthy and FM group in one cluster for each group. In the healthy control group, the centroid dipole was located in the left medial frontal gyrus (Talairach coordinates: $X = -4$, $Y = 56$, $Z = -5$), whereas in the fibromyalgia group, the centroid dipole was located in the right middle temporal gyrus (Talairach coordinates: $X = 67$, $Y = -23$, $Z = -5$).

Between-group differences (fibromyalgia vs. healthy control group) showed differences during dual- and single-task conditions. During dual-task conditions, the centroid dipoles were located in the right cuneus (Talairach coordinates: $X = 11$, $Y = -73$, $Z = 15$) and right medial frontal gyrus (Talairach coordinates: $X = 1$, $Y = 58$, $Z = -12$). During single-task conditions, the centroid dipole was located in the right medial frontal gyrus (Talairach coordinates: $X = 8$, $Y = 48$, $Z = 7$).

DISCUSSION

The main purpose of this study was to explore the neurophysiological response of women with FM and healthy controls while performing a DT (motor–cognitive). Significant differences were obtained in the healthy control group between ST and DT in the theta, alpha, and beta frequency bands. Nevertheless, significant within-group differences were not obtained in women with FM between ST and DT in any of the frequency bands. In addition, between-group differences were found in the alpha and beta frequency bands between healthy and FM groups, with lower values of beta and alpha in the FM group. Therefore, significant group*condition interactions were detected in the alpha and beta frequency bands. Regarding physical condition performance, between groups, analyses showed that women with FM obtained significantly worse results in the arm curl test than healthy controls, in both ST and DT.

Previous studies have reported differences between healthy controls and women with FM in the EEG signal at rest (Fallon et al., 2017; Villafaina et al., 2019a). However, this is the first study reporting differences between healthy controls and women with FM during DT conditions. Previous investigations have explored the brain activity while dual-tasking. Most of these studies have used the functional near-infrared spectroscopy

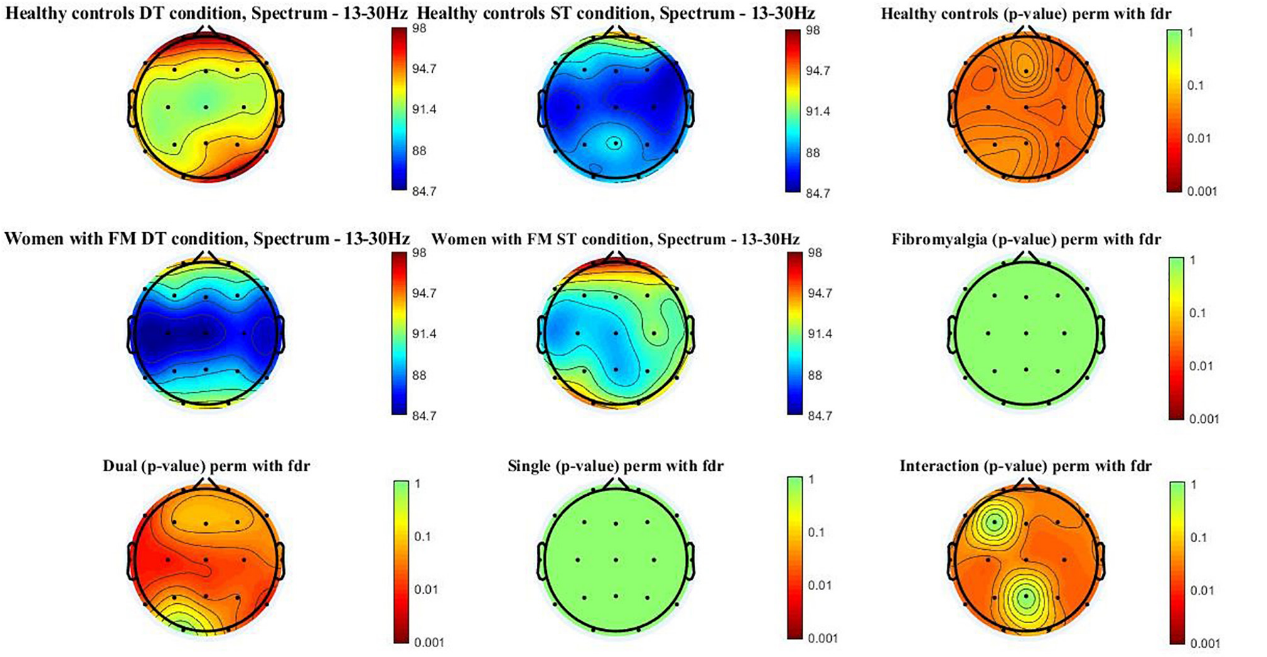

FIGURE 3 | Beta power spectrum (13–30 Hz) topographic maps in women with FM and healthy controls. Differences were only located ($p < 0.05$) between ST and DT conditions in healthy controls and between healthy controls and women with FM in the DT condition. In addition, the interactions group*condition is significant in the following scalp locations: frontal (Fp1, Fp2, Fz, F4, F7, and F8), central (Cz, C3, and C4), temporal (T3, T4, T5, and T6), parietal (P3 and P4), and occipital (O1).

(fNIRS) (Holtzer et al., 2011, 2015; Al-Yahya et al., 2016; Lin and Lin, 2016; Maidan et al., 2017) over the prefrontal cortex to investigate this topic. In this regard, increases in oxygen levels in the prefrontal cortex have been reported when performed any type of DT (Holtzer et al., 2015; Al-Yahya et al., 2016; Lin and Lin, 2016). However, results from fNIRS studies are limited to the prefrontal area due to the restricted number of channels that could be recorded. Thus, previous studies have employed the EEG to study the impact of DT on brain activity (De Sanctis et al., 2014; Malcolm et al., 2015; Bogost et al., 2016). Our results are consistent with a previous study where an increase in theta and beta power spectrum were observed between ST and DT (Pizzamiglio et al., 2017) in the frontal and parietal regions in healthy adults.

However, in the study of Pizzamiglio et al. (2017), a decrease in the alpha power spectrum during the DT was detected when compared with the ST condition. This is inconsistent with our results, where a significant increase in the DT was found in the healthy control group when compared with the ST condition. However, hypothetically, it could be due to the type of DT, which is presented in this study (a memory-based DT, which consisted of remembering three random unrelated words while the women were performing the tests). In this regard, findings of alpha power have not been consistent across experimental studies (Wianda and Ross, 2019). In our study, participants were encouraged to keep in mind these unrelated words while performing the motor task. This could be connected with the findings of a previous study where an alpha increase during the retention interval in a short-term memory task was reported (Jensen et al., 2002). Interestingly, another study has suggested that the increase in alpha power spectrum plays an active role in preventing the distracting information into areas which retain the memory items (Mazaheri et al., 2014). Moreover, previous studies have linked beta band to short-term memory (Tallon-Baudry et al., 1999; Palva et al., 2011), elevated mental workload (Coelli et al., 2015), or concentration (Kakkos et al., 2019) as well as increasing in working memory (Spitzer and Haegens, 2017). In the same line, the theta band is associated to increases in cognitive workload (Fuentes-García et al., 2019; Diaz-Piedra et al., 2020). Therefore, further investigation is needed to clarify the role of alpha, beta, and theta bands in different types of DT conditions.

The arm curl provides useful information in people with fibromyalgia since it could potentially be used to discriminate (in ST conditions) women with fibromyalgia from healthy women (Ariadna Aparicio et al., 2015) or even the severity of the symptoms (Soriano-Maldonado et al., 2015). Our results showed differences between women with FM and healthy controls in both ST and DT in this physical fitness test. Nevertheless, within-group differences were not observed in women with FM nor healthy controls in the ST or DT conditions. These results are consistent with previous investigations where similar results using both the arm-curl test and the same simultaneous cognitive task were observed (Villafaina et al., 2019d). These results, as previously suggested by Villafaina et al. (2018), could be due to a low complexity of the motor task. However, since the arm curl test has not been deeply studied under DT conditions in women with FM, further studies are necessary to confirm this hypothesis.

However, neurophysiological results showed that healthy controls modified their brain activity between ST and DT in order to adapt their brain activity to the task commitment. These changes were not observed in the women with FM between the ST and the DT conditions. This could be derived from the attention deficit disorder (van Rensburg et al., 2018; Yilmaz and Tamam, 2018), which is common in this population. Besides, people with FM usually showed depression or cognitive impairment (Wolfe et al., 2010) in several domains such as long-term memory (Canovas et al., 2009), short-term memory (Park et al., 2001), or working memory (Coppieters et al., 2015). These comorbidities could have an impact on EEG, showing a left hemisphere hypoactivation (Villafaina et al., 2019e) or a reduced theta power at rest (Musaeus et al., 2018; Villafaina et al., 2019b). However, taking into account the simultaneous cognitive task, the attention deficit disorder could have a significant impact on the EEG patter during the DT condition. The attention deficit disorder could lead to difficulties in focusing their attention on three unrelated words provided before the test started, "forgetting" to think in these words during the DT condition. This, hypothetically, may explain that changes in the neurophysiological measures were not found. For instance, it could be expected, as occurred in the healthy group, that beta and theta bands would increase during the DT condition due to higher cognitive demands or workload (Fuentes-García et al., 2019; Diaz-Piedra et al., 2020). This is because increases in beta and theta bands, due to increases in cognitive workload, could be expected. Thus, EEG measurement could be an interesting tool to enhance the knowledge about the DT paradigm as well as help to interpret the reasons behind differences between healthy controls and women with FM in the physical performance in both DT and ST conditions.

Source analysis shows differences within group (ST vs. DT) in both healthy and FM groups. In the healthy control group, the centroid dipole was located in the right anterior cingulate, whereas in the fibromyalgia group, the centroid dipole was located in the left cingulate gyrus. In this regard, source analysis has been used to investigate the electrocortical source during ST and DT paradigms (Lin et al., 2011; Bogost et al., 2016). A previous study showed a reduction in the mean absolute N1 ERP peak amplitude in the DT compared with the ST in the N1 between ST and DT conditions (Bogost et al., 2016). However, the dual-task employed in this investigation (visual working memory) does not allow to compare the results. Thus, further investigation in this field is required.

This study has some limitations. First, all the participants were women, so results cannot be extrapolated to men with FM. In the same line, the relatively small sample size (17 women with FM and 19 healthy controls) could make that only greater differences would reach the significance level. Thus, results cannot be generalized and further research in this field is necessary. Third, the lack of test–retest reliability, validity, and variability of the EEG results should be considered. Therefore, an EEG register longer than 30 s should be recommended as well as the inclusion of a baseline assessment. Lastly, according to their current medical history any psychiatric or neurological diagnoses were present in their medical history. However, due to the high rate of comorbidities with several psychiatric disorders in FM (such as mood, anxiety, or depression) (Sancassiani et al., 2017) could not be discarded that some of the participants might be suffering from these disorders when women with FM were assessed. Taking into account these limitations, results should be taken with caution.

CONCLUSION

Neurophysiological differences between women with FM and healthy controls were found during DT condition. This is the first study which investigates the neurophysiological response of women with FM while simultaneously performing a motor and a cognitive task. Women with FM showed the same brain activity pattern during ST and DT conditions, whereas healthy controls seem to adapt their brain activity to task commitment.

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 Extremadura Bioethical Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JF-G, SV, and NG conceived the study. SV and RC-P collected the data. SV and RC-P analyzed the data. JF-G, NG, and SV designed the figures and tables. SV, JF-G, and NG wrote the manuscript. NG, SV, JF-G, and RC-P provided critical revisions on the successive drafts. All authors approved the manuscript in its final form.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.558849/full#supplementary-material

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The Influence of an Acute Exercise Bout on Adolescents' Stress Reactivity, Interference Control, and Brain Oxygenation Under Stress

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Background: High psychosocial stress can impair executive function in adolescents, whereas acute exercise has been reported to benefit this cognitive domain. The aim of this study was to investigate whether an acute bout of aerobic exercise improves the inhibitory aspect of executive function and the associated dorsolateral prefrontal cortex (DLPFC) oxygenation when under stress.

Methods: Sixty male high school students aged 16–20 years performed a Stroop task (baseline condition) and were randomly assigned to an exercise group (30 min on ergometer at 70% of maximum heart rate) and a control group (30 min of reading). Subsequently, all participants underwent a modified Trier Social Stress Test, which included a Stroop task under enhanced stress. The Stroop tasks in both conditions were combined with functional near-infrared spectroscopy to record changes in DLPFC oxygenation in response to the tasks. Stress reactivity was measured with saliva samples (cortisol, alpha-amylase), heart rate monitoring, and anxiety scores.

Results: All stress parameters indicated increases in response to the stressor ($p < 0.001$), with higher alpha-amylase [$t(58) = -3.45$, $p = 0.001$, $d = 1.93$] and anxiety [$t(58) = -2.04$, $p = 0.046$, $d = 0.53$] reactions in the control compared to the exercise group. Controlling for these two parameters, repeated measures analyses of covariance targeting changes in Stroop interference scores showed no main effect of stress [$F(1,58) = 3.80$, $p = 0.056$, $\eta p^2 = 0.063$] and no stress × group interaction [$F(1,58) = 0.43$, $p = 0.517$, $\eta p^2 = 0.008$]. Similarly, there was no main effect of stress [$F(1,58) = 2.38$, $p = 0.128$, $\eta p^2 = 0.040$] and no stress × group interaction [$F(1,58) = 2.80$, $p = 0.100$, $\eta p^2 = 0.047$] for DLPFC oxygenation.

Conclusion: Our study confirms potentially health-enhancing effects of acute exercise on some of the physiological and psychological stress reactivity indicators. However, our data do not support the notion of an effect on interference control and DLPFC activation under stress.

Keywords: executive function, inhibitory control, fNIRS, psychosocial stress, physical activity, TSST

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INTRODUCTION

The physiological response to acute stress is characterized by the activation of the hypothalamus-pituitary-adrenal (HPA) axis, which results in the release of cortisol by the adrenal cortex, and the autonomic nervous system (ANS), which increases the activity of its sympathetic division under stress and initiates a number of processes such as increased release of adrenaline and increase in heart rate (Pruessner et al., 2010). While there is a healthy midrange of stress reactivity that is considered adaptive and useful for coping with certain stressors (Boyce and Ellis, 2005), high stress reactivity can be problematic, as it contributes to allostatic load (McEwen, 1998) and is associated with health concerns. As a recent systematic review revealed, higher levels of stress reactivity are associated with negative long-term effects on health, and in particular with increased risk of cardiovascular disease and immune system dysfunction (Turner et al., 2020).

Studies have also shown that the brain is affected eminently by acute stress. Stress-related changes in architecture and function of the prefrontal cortex (PFC) in particular have been investigated, as it is involved in the regulation of the stress response, but also reacts sensitively to high stress exposure (McEwen and Gianaros, 2010). For instance, cortisol can cross the blood–brain barrier and bind to mineralocorticoid (MR) and glucocorticoid receptors (GR) in the PFC (Lupien et al., 2009), and stress-induced increases in catecholamine levels can indirectly impair PFC functioning as well (Arnsten, 2009). The PFC is considered the highest-evolved brain region, as its principal task is processing higher-order cognitive functions that enable thoughtful, rational and planned behavior (Pruessner et al., 2010; Diamond, 2013). As a part of this, executive functions refer to top-down mental processes requiring working memory, cognitive flexibility or inhibitory control (Diamond, 2013). During homeostasis, behavior is largely regulated through these top-down processes. However, under acute psychological stress, function of the PFC is impaired, and a shift takes place from thoughtful, time-consuming top-down to sensory-driven, rapid bottom-up regulatory processes (Arnsten, 2009). In support of this shift in regulation, meta-analytic findings have shown that behavioral performance in tasks requiring working memory, cognitive flexibility or interference control is impaired under acute stress (Shields et al., 2016).

Interference control, as an important subtype of inhibition, can be assessed with the Stroop color-word task. This task consists of two conditions, where color words are presented either in compatible or incompatible ink color, and requires participants to react to the ink color while ignoring the meaning of the written word. The time delay and/or the increased number of errors caused by the conflict in the incompatible condition is called the Stroop interference effect (Vanderhasselt et al., 2009). Neuroimaging studies suggest that among different brain regions, the dorsolateral prefrontal cortex (DLFPC) in particular is activated during Stroop tasks. This has been associated with the upregulation of the attentional set in order to process the stimulus interference on incompatible trials (Vanderhasselt et al., 2009). Additionally, in studies employing functional near-infrared spectroscopy (fNIRS), better Stroop performance (i.e., less interference) has been associated with the dominance of left-lateralized DLPFC activation (Zhang et al., 2014; Ludyga et al., 2019a).

As recent research has shown, adolescents are particularly at risk of experiencing negative effects of stress on cognition. According to the World Health Organization and national psychological health surveys (American Psychological Association, 2014; Güntzer, 2017; World Health Organization, 2019), adolescents have to cope with an increasing number of psychosocial stressors, while their physiological stress response mechanisms and psychological coping strategies are still developing. It is unsurprising that better stress coping strategies were the main health need reported by Swiss adolescents (Jeannin et al., 2005). Moreover, adolescents have been reported to have higher stress reactivity than other age groups (Romeo, 2010), and there are indications that adolescents might be particularly vulnerable to negative effects of stress on the prefrontal cortex (Lupien et al., 2009). This highlights the need for research on factors that can potentially mitigate negative effects of acute stress on executive functioning in this age group.

In this regard, the investigation of the effects of an acute exercise bout seems promising for a number of reasons. Firstly, moderate acute aerobic exercise has been found to elicit small-to-moderate improvements in inhibitory control and other executive functions (Ludyga et al., 2016). In adolescents, these temporary improvements appear to last at least 60 min after cessation of the exercise session (Ludyga et al., 2019b). Moreover, some studies suggest that acute exercise benefits interference control via increased oxygenation of the DLPFC. Using fNIRS, Ji et al. (2019) and Endo et al. (2013) showed that positive effects of acute exercise on Stroop performance were accompanied by changes in DLPFC oxygenation, and several studies reported that acute exercise at mild (Byun et al., 2014) or moderate intensity (Yanagisawa et al., 2010) evoked a predominantly left-lateralized activation of the DLPFC, also associated with improved Stroop performance. This suggests that acute exercise benefits interference control via a change toward a dominance of the left DLPFC. Secondly, researchers have suggested that exercise has stress-modulating properties. According to the Cross-Stressor-Adaptation Hypothesis, exercise causes stress-like reactions in the human body, and repeated exercise has been shown to cause a reduction of the stress response to exercise (habituation) (Hackney, 2006), which can potentially transfer to other stressors as well (Sothmann, 2006). Systematic reviews of the literature showed that study results on such transfer effects to psychosocial stress are still inconclusive (Jackson and Dishman, 2006; Mücke et al., 2018). However, cross-sectional studies (e.g., Rimmele et al., 2007), and a randomized controlled trial (Klaperski et al., 2014) using the Trier Social Stress Test (TSST), a psychosocial stressor task with high effectivity, reliability and ecological validity, showed attenuated stress reactivity of the HPA axis and the ANS in fitter participants and in those who participated in an exercise program, respectively. Moreover, initial evidence suggests that similar effects already occur after a single bout of aerobic exercise (Zschucke et al., 2015). Accordingly, acute exercise could mitigate potential negative effects of psychosocial stress on executive functioning via two different pathways—either by facilitating executive functioning, or by reducing the magnitude of the reaction to the stressor.

Therefore, the primary aim of the present study was to examine the effects of an acute bout of moderate aerobic exercise on interference control under the influence of psychosocial stress in male adolescents. Studies have found increased performance in interference control to be associated with more left-lateralized activation of the dorsolateral prefrontal cortex (Yanagisawa et al., 2010; Byun et al., 2014). Accordingly, it was hypothesized that compared to a control condition, acute exercise mitigates negative effects of stress on interference control, and is therefore associated with better behavioral interference control and more left-lateralized DLPFC activation than the control condition. As a secondary aim, the effects an acute bout of aerobic exercise on stress reactivity were investigated.

MATERIALS AND METHODS

Participants

In total, 60 participants were recruited via advertisements, flyers and personal contact. Only male, healthy, right-handed (as verified with the Edinburgh Handedness Inventory, Oldfield, 1971) persons between 16 and 20 years of age were included. All participants were fluent German speakers. To standardize educational status, only participants currently attending academic high schools were admitted. Other studies showed that the level of regular physical activity can influence stress reactivity (Klaperski et al., 2014). Therefore, only participants who were not completely inactive, but who reported between two and six hours of exercise per week were included. Participants were informed about the study procedures at least 3 days prior to the data assessment and provided informed consent. All study procedures were in accordance with ethical principles of the Declaration of Helsinki and approval was obtained by the local ethics committee (Ethikkommission Nordwest- und Zentralschweiz, project number: 2018-01775) before the start of the study.

Study Design

The study design is depicted in **Figure 1**. Participants were randomly assigned to the exercise group ($N = 30$) or the control group ($N = 30$). The amount of self-reported regular physical activity was used as a stratum in order to create groups with similar physical activity behavior. As a cut-off, an amount of vigorous physical activity (VPA) of 180 min per week, as reported in the International Physical Activity Questionnaire (IPAQ), was used. This cut-off was chosen because it was the average weekly VPA in a previous study with a very similar sample (Mücke et al., 2020). All appointments were scheduled in the afternoon at either 13:00 or 16:00 to minimize the potential impact of variations in diurnal cortisol levels (Kudielka et al., 2004). Upon arrival, participants rested for 15 min to reduce the influence of possible stress factors before and/or during arrival. Body height and weight were then measured objectively with a stadiometer and an electronic scale (Tanita BC-601, Tokyo, Japan), respectively, and participants filled in a questionnaire including age (in years), socio-economic status (one item), physical activity [International Physical Activity Questionnaire (IPAQ); Craig et al., 2003], sleep complaints [7-item Insomnia Severity Index (ISI); Gerber et al., 2016], chronic stress [10-item Perceived Stress Scale (PSS); Klein et al., 2016], mental toughness [18-item short form of the Mental Toughness Questionnaire (MTQ18); Gerber et al., 2018], and psychopathology [25-item Strengths and Difficulties Questionnaire (SDQ); Goodman, 2001]. The validity of all psychological instruments has been established previously and all measures showed acceptable internal consistency in the present sample (Cronbach's alpha > 0.67 for all psychometric variables). Subsequently, an fNIRS head cap (NIRSport, NIRx Medical Technologies, Berlin, Germany) was fitted to the participants' head, sensors were calibrated and a Stroop Color-Word task was performed (these processes are described in detail in Section "Interference Control and Prefrontal Brain Activity"). During the next 30 min, the control group read an article from a magazine of their choice, while the exercise group performed an exercise session at moderate intensity on a bicycle ergometer (R60, Vision Fitness, Frechen, Germany). After the intervention, the head cap was mounted again. Subsequently, a modified version of the Trier Social Stress Test (TSST) was performed as described in Section "Stress Paradigm and Measurement of Stress Reactivity". The time delay between the end of the exercise or control condition and the beginning of the stress task was approximately 10 min. Within the TSST setup, the Stroop Color-Word task was performed again, with the difference that this time participants were instructed in a way that contributed to an increase in psychosocial stress (see Section "Stress Paradigm and Measurement of Stress Reactivity"). The appointment ended with a 10 min resting period, and all participants received a financial compensation of 70 CHF for their participation. Before and after the Stroop tasks, the intervention (acute exercise vs. reading) and the stress test, and after the resting period, saliva samples were collected with Salivette Blue Cap (Sarstedt, Nümbrecht, Germany) to control for saliva cortisol and alpha-amylase levels (see **Figure 1** and Section "Stress Paradigm and Measurement of Stress Reactivity").

Exercise Session

During the exercise session, participants pedaled at a constant speed (70–80 rpm). Moderate intensity was defined as 70% of maximum heart rate (HR_{max}), which was calculated with the formula $HR_{max} = 208 - 0.7 \times \text{age}$ (Tanaka et al., 2001). Pedaling resistance was continuously adjusted according to the measured heart rate. Furthermore, subjectively perceived intensity was monitored every 5 minutes using rating of perceived exertion (Borg, 1982).

Interference Control and Prefrontal Brain Activity

A computer-based version of the Stroop Color-Word task was used to assess interference control (Homack and Riccio, 2004). It consisted of compatible and incompatible trials. In compatible trials, color words appeared in the same ink color (e.g., "blue" printed in blue), whereas in incompatible trials, color words appeared in a different color of ink (e.g., "yellow" printed in green). To ensure similar visual content, the German color words "grün" (green), "gelb" (yellow), "blau" (blue), and "pink" were

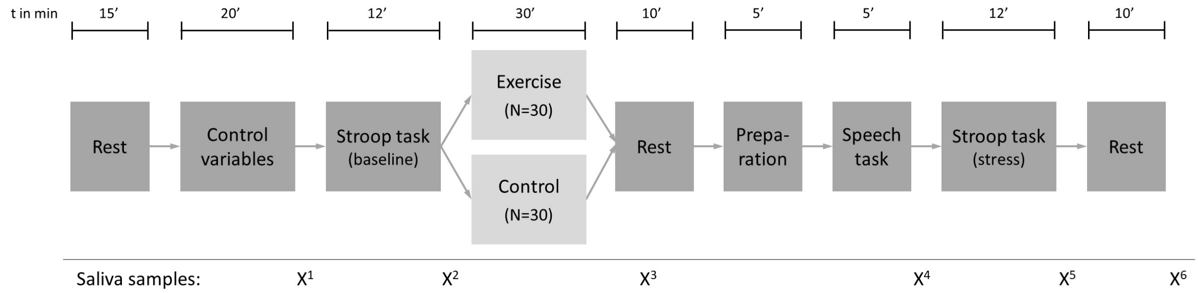

FIGURE 1 | Study design.

used. Participants were instructed to press a button corresponding to the color of ink, ignoring the actual meaning of the word, and to react as quickly and accurately as possible. Stimuli were presented for 250 ms, and responses were collected within a 1250 ms time window. The inter-stimulus time varied randomly between 300 and 500 ms. The task included twenty test blocks, each lasting 22-24 s. The duration of the resting periods between the test blocks varied randomly between 10 and 15 s. Compatible and incompatible test blocks alternated and within each block, the stimuli appeared with equal probability and followed a fully randomized order. Before testing, two practice blocks were conducted for familiarization and to reduce learning effects. Illustrations of the Stroop task sequence and block design are presented in the **Supplementary Material** (**Supplements 1, 2**).

For analysis, an interference score was calculated as the difference between reaction time on incompatible trials minus reaction time on compatible trials. Only response-correct trials with reaction times ≥120 ms were used for calculation as shorter response times would be highly likely to indicate guesswork (Zhang et al., 2014). A lower interference score equals higher interference control. To check whether potential group differences were influenced by speed-accuracy trade-offs, response accuracy was recorded as well.

For measurement of DLPFC brain oxygenation during the Stroop task, a dual-wavelength (760 and 850 nm) continuous-wave fNIRS system with a sampling rate of 7.8125 Hz (NIRSport, NIRx Medical Technologies, Berlin, Germany) and the recording software NIRStar 15.2 (NIRx Medical Technologies, Berlin, Germany) were used. Eight optodes (4 illumination sources, 4 light detectors) were mounted into a flexible cap, which was then placed on the participant's head. Optodes were equally distributed over the left and right DLPFC as shown in **Figure 2**. The DLPFC location was defined as described by Carlén (2017), and international 10:10 EEG positions were used as referencing points [for exact probe positions, see **Supplementary Material** (**Supplement 4**)]. The same montage has been used previously by Ludyga et al. (2019a). Spacers were used to keep the inter-optode distance constant at 3cm, which is considered the best compromise between high light penetration depth and sufficient signal-to-noise ratio (Ferrari and Quaresima, 2012; Tak and Ye, 2014). A black overcap was used to minimize the impact of ambient light. Additionally, the surrounding noise was reduced to a minimum and participants were instructed to avoid head movements and speaking during the Stroop task. Recording procedures were in line with existing quality standards (Orihuela-Espina et al., 2010) and recommendations for fNIRS assessments in exercise-cognition research (Herold et al., 2018).

After recording, fNIRS data was processed with Homer2 version 2.3 (Huppert et al., 2009). The processing stream followed the one proposed by Brigadoi et al. (2014) and is described in detail in Ludyga et al. (2019a). Artifacts exceeding defined thresholds were automatically marked and manually verified. Based on the results of systematic comparisons of artifact correction techniques (Scholkmann et al., 2010; Cooper et al., 2012), spline interpolation was used to correct marked artifacts, followed by a frequency filter with a low cut-off at 0.01 Hz (Yennu et al., 2016) and a high cut-off at 0.5 Hz (Brigadoi et al., 2014). Block averages were created for compatible and incompatible test blocks with the 2 s period preceding the test block used as reference. For the calculation of left and right DLPFC oxygenation, the average of all 4 channels on each side was calculated because test-retest reliability has been found to be higher at cluster level compared to individual channels (Schecklmann et al., 2008). Oxygenation related to Stroop interference was calculated as average oxygenation during incompatible minus compatible test blocks (Δ_{OXY}).

Stress Paradigm and Measurement of Stress Reactivity

Psychosocial stress was induced using a modified version of the TSST (Kirschbaum et al., 1993). It consisted of an anticipation phase and a mock job interview, followed by a Stroop task with adapted instructions designed to enhance psychological stress. Both the mental arithmetic task used in the original TSST, as well as the Stroop task implemented in our modified version, have been used as cognitive stressors in previous studies (Dickerson and Kemeny, 2004). In our psychosocial stressor, two motivated performance tasks (speech and cognitive test) were combined with the additional element of uncontrollability and socio-evaluative threat. This combination has been shown to be more effective in triggering a physiological stress response than other laboratory stressors consisting only of a single task (Dickerson and Kemeny, 2004). The following protocol was used: after a 5 min preparation phase, participants performed a 5 min unrehearsed speech in front of a committee of two (one male

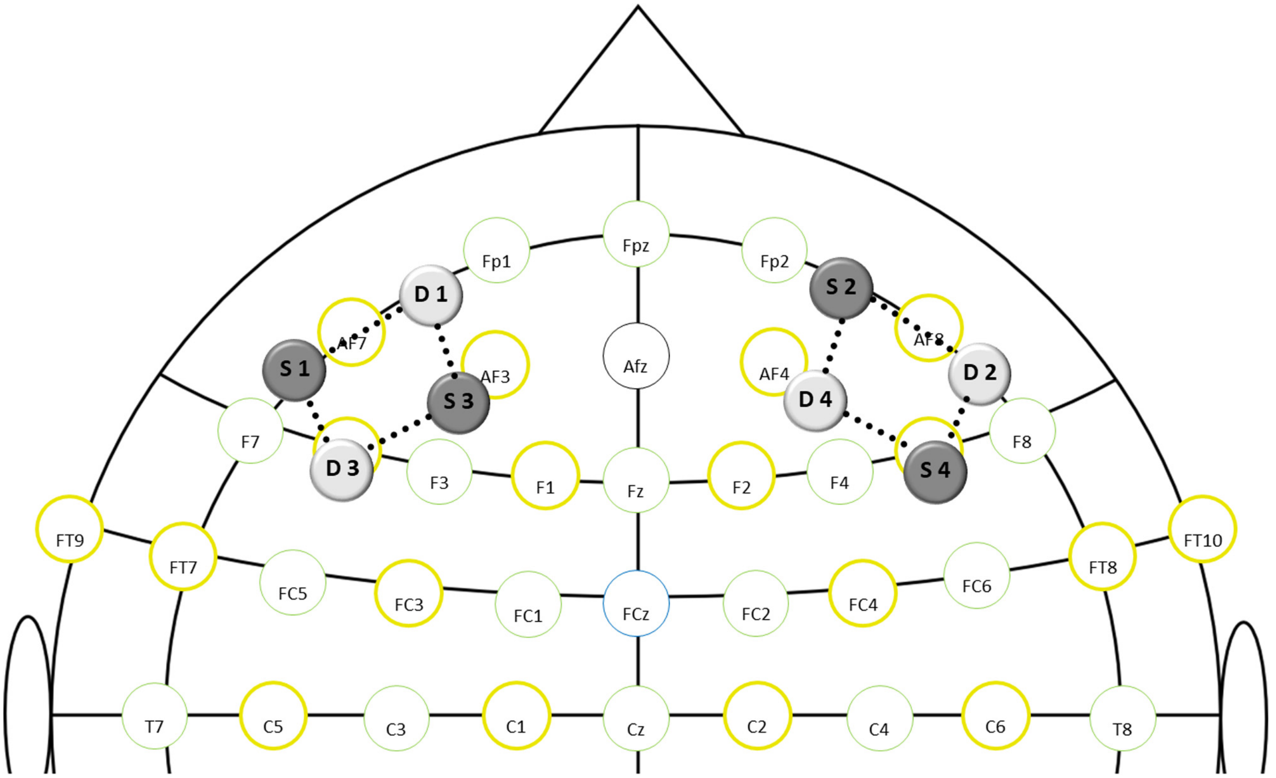

FIGURE 2 | fNIRS montage layout in relation to standard EEG positions (S-source; D-detector; dotted lines-channels).

and one female), followed by a 10 min Stroop task. Participants were instructed to imagine a situation in the near future when they finished school, were looking for a job and were offered an interview for their dream job. The committee was introduced to the participants as the manager of the company and an assistant who is specialized in the interpretation of body language and voice frequency. Throughout the speech, the committee showed neutral facial expressions and only used standardized responses (e.g., "You still have time left. Please continue."). Subsequently, the Stroop task was performed as described in the section above, with the following additions. The committee informed the participant that his test performance was visible on their screen and that they were able to compare his performance directly to other participants' data. The committee further remarked that if he did not perform well, he would not get the job, and the financial compensation for study participation would be reduced.

Stress reactivity was measured using saliva samples (for analysis of cortisol and alpha-amylase concentrations), heart rate monitoring and self-reported state-anxiety scores. While salivary free cortisol represents the reactivity of the HPA axis (Kudielka et al., 2004), salivary alpha-amylase is known to be reflective of the stress response of the autonomic (more specifically: sympathetic) nervous system (Nater and Rohleder, 2009). Saliva samples were collected at several time points during the appointment as shown in **Figure 1**. After data assessment, they were first stored at −20°C and then sent to the Biochemical Laboratory of the University of Trier, Germany, for analysis of cortisol (in nmol/l) and alpha-amylase (in U/ml) concentrations using time-resolved fluorescence immunoassay. As a parameter indicating the activation of the sympathetic nervous system in reaction to stress, heart rate was monitored continuously throughout the stress test. For the purpose of data analysis, 1 min intervals were averaged. Baseline heart rate was measured for 2 min before introduction of the stress test. Psychological stress reactions were measured before and after the stressor using 5 items of the state-anxiety scale of the State-Trait Anxiety Inventory (STAI; Laux et al., 1981; Cronbach's alpha = 0.72). After recoding inverted items, a sum score was calculated. It ranges from 5 to 20, with higher scores indicating higher anxiety.

Statistical Analysis

A power analysis was calculated with G*Power software. As no data on the effects of acute exercise on interference control under stress exists, yet, our power analysis was based on a meta-analysis by Verburgh et al. (2014), who reported moderate effects of acute exercise on interference control in adolescents. It resulted in a minimum number of 52 participants (parameters: repeated measures ANOVA, within-between interaction; effect size f = 0.20; alpha error probability = 0.05; power = 0.80; number of groups: 2; number of measurements: 2; correlation among repeated measures = 0.50; non-sphericity correction = 1).

Following Pruessner et al. (2003), for physiological stress reactivity (cortisol, alpha-amylase and heart rate reactivity), the area under the curve with respect to the increase (AUC_I) was calculated. Since alpha-amylase shows an immediate increase after stimulation of the ANS (Nater and Rohleder, 2009), samples 3–6 (**Figure 1**) were used. Salivary cortisol levels usually rise with about 10 min delay relative to stressor onset (Foley and Kirschbaum, 2010). Therefore, samples 4–6 were used to assess cortisol reactivity. For heart rate reactivity, the 2 min before the introduction of the TSST were averaged and used as a baseline, and the AUC_I was calculated from the subsequent averaged 1 min intervals until stressor cessation. Psychological stress reactivity was defined as the difference of the post-stress minus pre-stress anxiety score. Subsequently, potential group differences in baseline values and stress reactivity (AUC_I) were analyzed using separate independent T-tests.

The effect of exercise (compared to the control condition) on interference control under stress was examined using a repeated-measures analysis of variance (rANOVA) with stress (baseline Stroop interference vs. Stroop interference under stress) as within-subject variable and group (exercise vs. control) as between-subjects factor. In a second run of the analysis, stress reactivity parameters that showed group differences were added as covariates.

The effect of exercise on DLPFC oxygenation under stress was investigated using a rANCOVA with stress (Δ_{OXY} at baseline vs. Δ_{OXY} under stress) and hemisphere (Δ_{OXY} left vs. Δ_{OXY} right DLPFC) as within-subject variables and group (exercise vs. control) as between-subject factors. Heart rate during the Stroop task was added as a covariate, because fNIRS data can potentially be affected by systemic changes (Herold et al., 2018). For all rAN(C)OVA, main effects and interactions were reported. Effect sizes were classified as small ($d \geq 0.2$; $\eta p^2 \geq 0.01$), medium ($d \geq 0.5$; $\eta p^2 \geq 0.06$), or large ($d \geq 0.8$; $\eta p^2 \geq 0.14$) (Cohen, 1988). An alpha level of $p \leq 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS 26 (IBM Corporation, Armonk, NY, United States).

RESULTS

Sample Characteristics and Exercise Session

Characteristics of the sample are presented in **Table 1**. The exercise and control groups did not differ significantly in any of the anthropometric, sociodemographic or psychological control variables. During the exercise session, the average (standard deviation) heart rate and rating of perceived exhaustion were 128.5 (7.9) beats per minute and 14.0 (1.0), respectively. Average heart rate during the exercise session was significantly higher compared to the control condition [69.8 (10.0) beats per minute; $t = 24.9$, $p = 0.000$, $d = 6.60$] and represented 65.7 (4.0)% of HR_{max}.

Stress Reactivity

To enable the investigation of interference control under stress, our study design required differences in stress parameters between both Stroop task conditions (baseline and under-stress). As a manipulation check, paired T-tests were calculated. All physiological stress parameters indicated higher stress during the Stroop task performed under stress compared to the baseline condition (for cortisol and alpha-amylase directly after both Stroop tasks: $p < 0.001$; for heart rate during both Stroop tasks: $p = 0.03$). When using the measurement points directly after each Stroop task, self-reported psychological stress did not differ between both conditions ($p = 0.80$). However, between both measurement points, the stress test did evoke a measurable psychological stress response (see below).

TABLE 1 | Comparison of group characteristics (independent T-test).

	Exercise group M ± SD	Control group M ± SD	p
Age in years	17.9 ± 1.2	17.9 ± 1.3	0.999
BMI in kg/m^2	22.9 ± 3.1	22.8 ± 3.2	0.944
Socioeconomic status	3.3 ± 0.6	3.2 ± 0.6	0.667
MVPA in min/week (IPAQ)	308.3 ± 237.4	288.7 ± 157.8	0.707
Chronic stress (PSS)	13.9 ± 4.5	15.0 ± 5.3	0.365
Mental toughness (MTQ18)	45.6 ± 7.3	46.2 ± 6.8	0.730
Psychopathology (SDQ)	9.23 ± 4.1	9.23 ± 4.4	0.999
Insomnia (ISI)	7.6 ± 5.0	6.3 ± 4.1	0.304

BMI, body mass index; IPAQ, International Physical Activity Questionnaire; ISI, Insomnia Severity Index; M, mean; MTQ18, Mental Toughness Questionnaire; MVPA, Moderate-to-vigorous physical activity; PSS, Perceived Stress Scale; SD, standard deviation; SDQ, Strengths and Difficulties Questionnaire.

Changes in physiological and psychological stress parameters in response to the modified TSST are depicted in detail in **Figure 3**. Comparing both groups, independent T-tests revealed no baseline difference (that is: after exercise or control intervention, before stress test) for cortisol ($t = -0.07$, $p = 0.943$, $d = 0.02$) and alpha-amylase ($t = 0.11$, $p = 0.914$, $d = 0.03$). However, the control group showed significantly less anxiety ($t = 2.55$, $p = 0.014$, $d = 0.67$) and lower heart rate ($t = 5.57$, $p < 0.001$, $d = 1.46$) before the stress task than the exercise group. With regard to stress reactivity, we found a significant increase across the total sample in all four parameters ($p < 0.001$). However, groups differed in stress responses of alpha-amylase [$t(58) = -3.45$, $p < 0.001$, $d = 1.93$] and anxiety [$t(58) = -2.04$, $p = 0.046$, $d = 0.53$], with large and medium effect sizes, respectively, indicating higher stress reactivity in the control group. No differences between the exercise and control groups were present for cortisol [$t(58) = -0.43$, $p = 0.668$, $d = 0.11$] and heart rate reactivity [$t(57) = -0.48$, $p = 0.636$, $d = 0.13$].

Inhibitory Performance

Figure 4 depicts the reaction times and interference scores for both groups during the baseline Stroop task and the Stroop task under stress. With regard to effects of exercise, and stress, on interference scores, the rANOVA showed no statistically significant main effect of stress [$F(1,58) = 0.01$, $p = 0.925$, $\eta p^2 = 0.000$] and no stress × group interaction [$F(1,58) = 0.05$, $p = 0.826$, $\eta p^2 = 0.001$]. After further including alpha-amylase and psychological stress reactivity, the rANCOVA again showed no statistically significant main effect of stress [$F(1,58) = 3.80$, $p = 0.056$, $\eta p^2 = 0.063$] and no stress × group interaction [$F(1,58) = 0.43$, $p = 0.517$, $\eta p^2 = 0.008$].

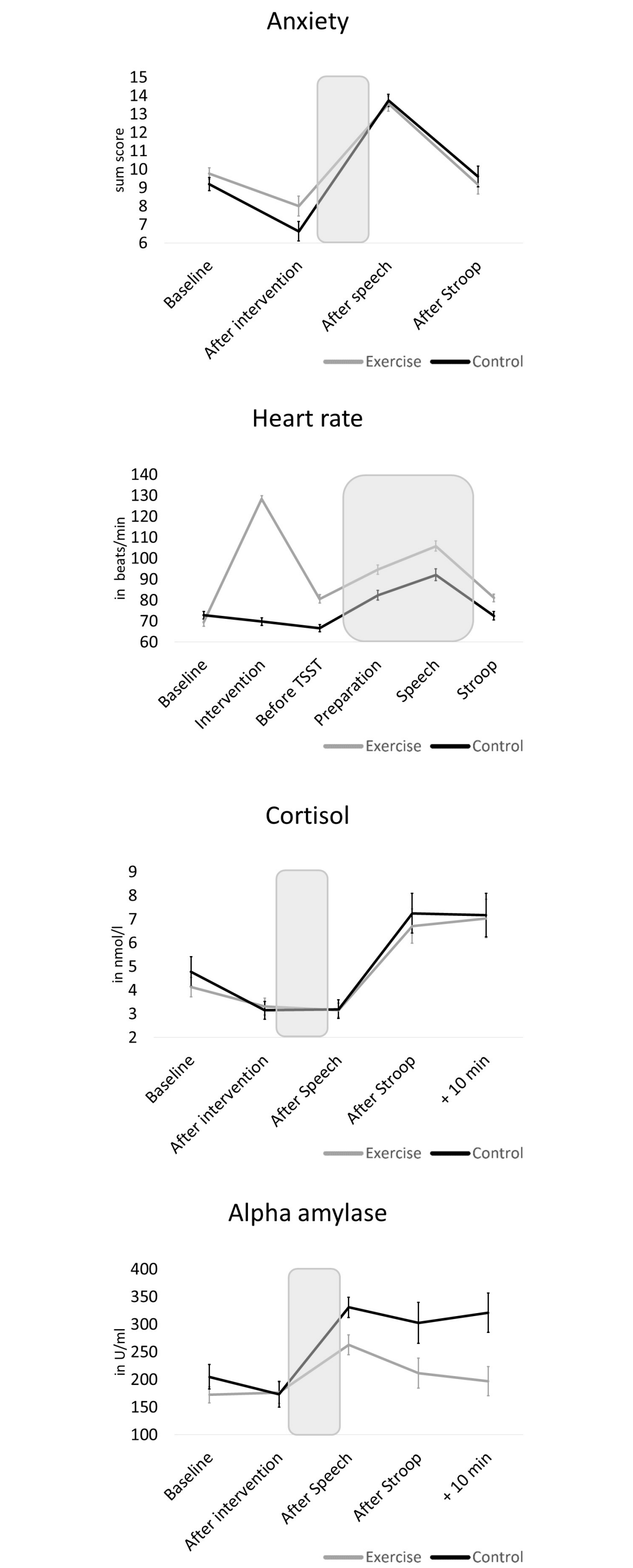

FIGURE 3 | Mean physiological and psychological stress reactivity of the exercise group and the control group. The shaded areas indicate the stressor (preparation and speech task). Error bars are standard errors of the mean (SEM).

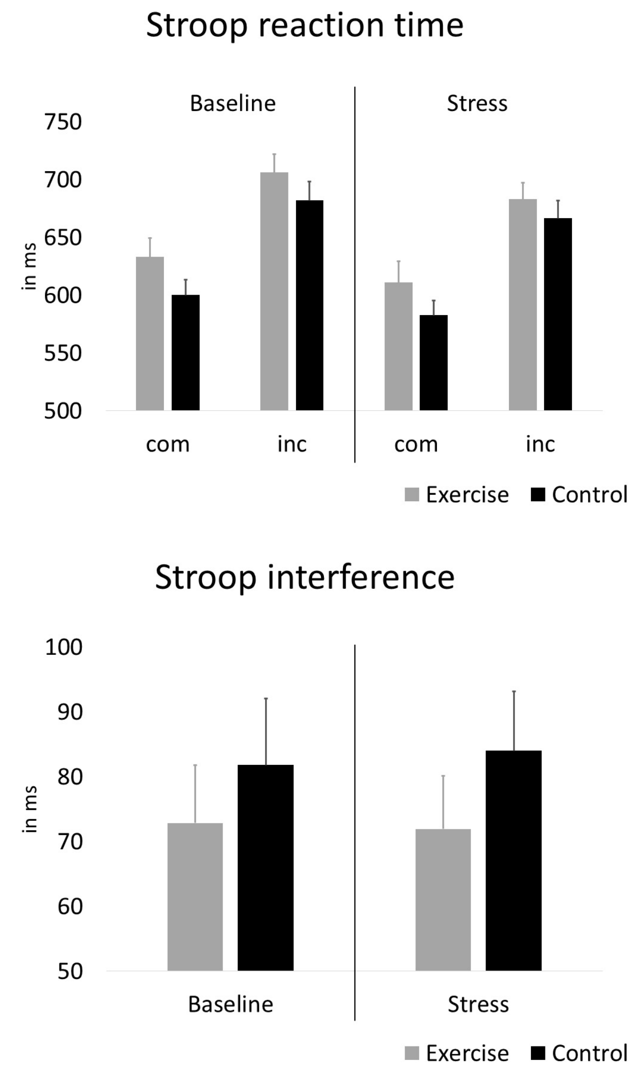

FIGURE 4 | Average Stroop reaction time during compatible (com) and incompatible (inc) test blocks and interference scores before and under stress. Error bars are standard errors of the mean (SEM).

Furthermore, response accuracy interference was analyzed to control for potential speed-accuracy trade-offs. Repeating the same analyses with response accuracy revealed no statistically significant main effect of stress [$F(1,58) = 1.826$, $p = 0.182$, $\eta p^2 = 0.031$] and no stress × group interaction [$F(1,58) = 3.79$, $p = 0.056$, $\eta p^2 = 0.061$]. However, at baseline the exercise group showed lower response accuracy during incompatible trials compared to the control group [$T(1,58) = -2.65$, $p = 0.010$, $d = 0.70$]. Response accuracy scores of both groups are presented in the **Supplementary Material** (**Supplement 3**).

DLPFC Oxygenation

The rANCOVA showed no statistically significant main effect of stress [$F(1,58) = 2.38$, $p = 0.128$, $\eta p^2 = 0.040$], no stress × group interaction [$F(1,58) = 2.80$, $p = 0.100$, $\eta p^2 = 0.047$], and no hemisphere × group interaction [$F(1,58) = 0.76$, $p = 0.387$,

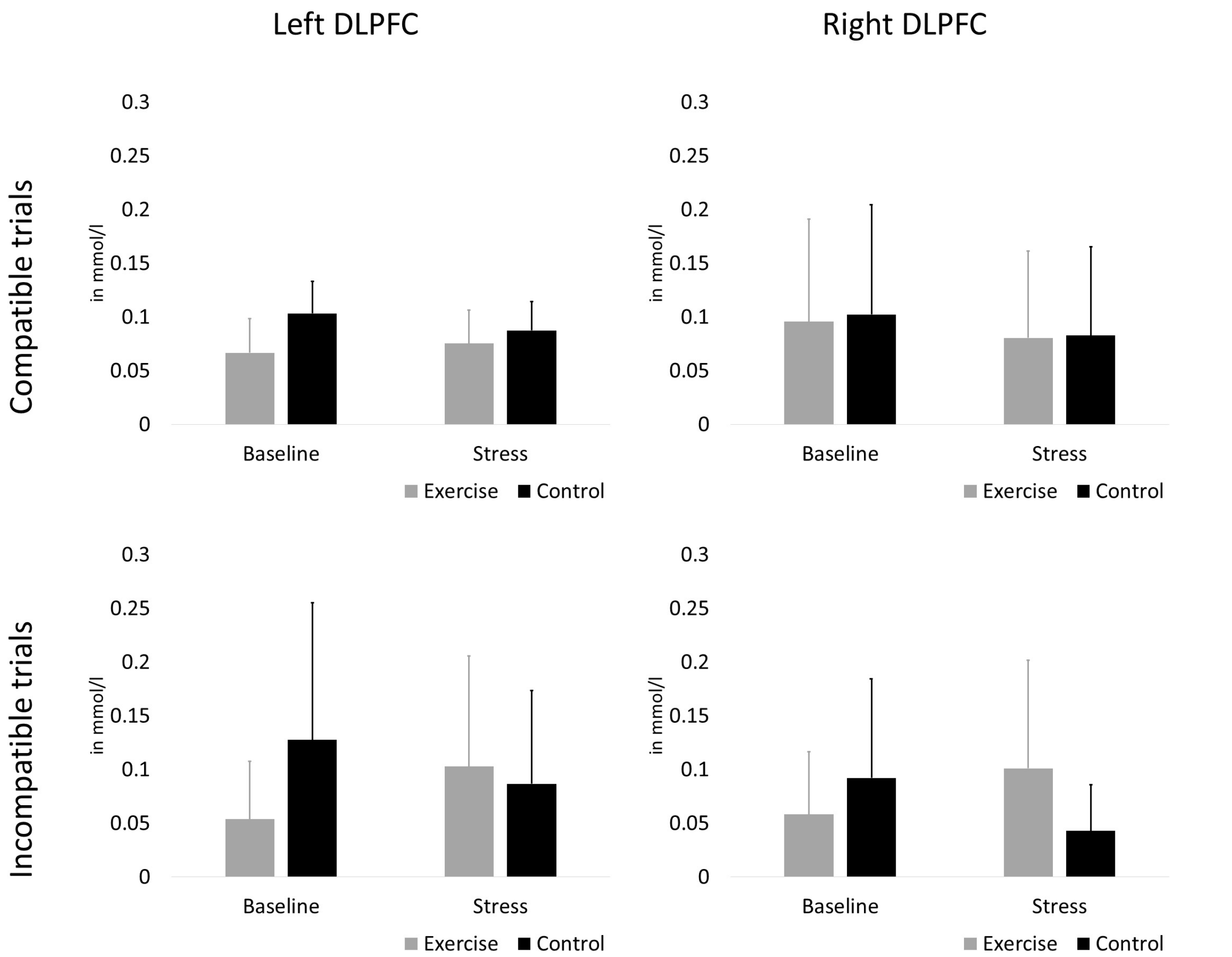

FIGURE 5 | Oxygenation changes in the left **(A,C)** and right **(B,D)**. DLPFC during compatible **(A,B)** and incompatible **(C,D)** test blocks. Error bars are standard errors of the mean (SEM).

$\eta p^2 = 0.013$]. All other main effects and interaction terms did not reach statistical significance ($p < 0.601$). Oxygenation changes in the left and right DLPFC during compatible and incompatible test blocks are presented in **Figure 5**.

DISCUSSION

This study aimed to investigate the effect of an acute exercise bout on interference control under stress and corresponding oxygenation differences in the left and right DLPFC. In our study, we found no indication of differences between the exercise group and control group with regard to interference control under stress, and controlling for differences in stress reactivity did not change this result. Corresponding oxygenation differences in left and right DLPFC also did not differ between groups. While the stress test elicited significant reactions in all stress reactivity parameters and across both groups, we found higher alpha-amylase reactivity and higher increases in anxiety in the control group compared to the exercise group.

Acute Exercise and Interference Control Under Stress

A wealth of studies have already investigated the effects of acute exercise on executive functioning without enhanced stress in various age groups. Systematic reviews and meta-analyses consistently reported small but significant effects, and demonstrated that acute exercise is beneficial for subsequent executive functioning across all age groups (Tomporowski, 2003; Chang et al., 2012; Ludyga et al., 2016), although age groups that are typically characterized by developmental changes seem to benefit more than others (Guiney and Machado, 2013; Ludyga et al., 2016). In a meta-analysis compiling data on preadolescent children (6-12 years), adolescents (13-18 years) and young adults (18-35 years), Verburgh et al. (2014) reported moderate effects of acute exercise on inhibition/interference control in children and adolescents, and small-to-moderate effects in young adults. More recent empirical findings on adolescents corroborated this pattern for interference control (Browne et al., 2016; Peruyero et al., 2017; Park and Etnier, 2019). However, no studies so far looked into the effects of acute exercise on interference control under the influence of psychosocial stress. Previous studies reported negative effects of acute stress on executive functions, including interference control (Shields et al., 2016). As maintaining high executive functioning under stress is of great importance for success in education and professional life, and higher executive functioning under stress has been shown to be associated with better health (Williams and Thayer, 2009; Shields et al., 2017), research on mitigating factors is important.

In this study, we present initial insights into the influence of acute exercise on interference control in the presence of acute psychosocial stress. Despite the promising effects on interference control in situations without additional stress, which previous studies reported to be most pronounced in young people, our study with participants in later stages of adolescence did not show such effects in the presence of acute psychosocial stress. However, these results, which refer to interference scores based on reaction time, can be influenced by differences in response accuracy. In our study, during incompatible trials the exercise group showed worse response accuracy at baseline, but not under stress, and a medium effect size (non-significant, however) pointed toward a stress × group interaction on accuracy interference, indicating potential group differences in response accuracy in favor of the exercise group. These potential group differences in response accuracy might indicate a speed-accuracy trade-off and might have caused effects on the main outcome to disappear. Nevertheless, compared to the results other studies reported for stress-free conditions, exercise effects on interference control appeared to be smaller or absent under stress, and based on our data, we cannot generally recommend acute exercise to enhance interference control under stress. Individuals differ largely in how they perceive and react to stress, and researchers argue that the vulnerability to, and resilience against potential negative effects of acute stress on cognition might vary largely among individuals (Sandi, 2013). While we took the most important anthropometric, sociodemographic and psychological confounders into account, it cannot be ruled out that among other individual factors, the effects of acute exercise were too small to be detected. Our exercise intervention comprised 30 min of ergometer exercise at a constant, moderate intensity (on average 66% of HR_{max}). While interventions of similar type, duration and intensity proved to be effective in enhancing interference control (Alves et al., 2012; Chang et al., 2015), it is possible that under acute stress, different exercise modalities might have yielded more favorable results. For instance, meta-analytical findings by Gu et al. (2019) indicate that open-skill exercise might be more effective for improving cognitive functioning than closed-skill exercise, and Ludyga et al. (2018) showed beneficial effects if aerobic and coordinative demands are combined. On the other hand, ergometer cycling seems to have superior effects on cognitive performance compared to treadmill running exercise (Lambourne and Tomporowski, 2010), and researchers found similar effects for aerobic and strength (Alves et al., 2012) or coordinative exercise (Ludyga et al., 2017) on inhibitory control. To elicit improvements in executive functioning, exercise durations between 20 and 60 min are deemed optimal (Tomporowski, 2003; Lambourne and Tomporowski, 2010). With regard to exercise intensity, studies reported beneficial effects on Stroop performance following low and high (Peruyero et al., 2017), and moderate intensity exercise (Browne et al., 2016; Park and Etnier, 2019). Studies investigating a dose-response relationship suggested an inverted-U-shaped effect, with best results for moderate exercise (McMorris and Hale, 2012). It is noteworthy that depending on intensity, exercise itself can have an impact on stress parameters. According to Hackney (2006), exercise that surpasses an intensity of 50-60% of the maximal oxygen uptake (VO_{2max}) increases circulating concentrations of cortisol. In our study, stress parameters did not rise in response to the exercise session (see **Figure 3**), which means that they might not have surpassed this VO_2 threshold. This might have had an influence on our results, and future studies should look into the effect of exercise intensity and exercise-induced stress on executive functions. Overall, the findings listed above apply to effects of different exercise modalities on executive functioning without the additional element of psychosocial stress, and future studies are encouraged to investigate whether different exercise modalities have distinct effects on executive functioning under stress.

The absence of the hypothesized beneficial effect of acute exercise in our study might in part be explained by the absence of the expected negative impact of stress on interference control. Our results showed no main effect of stress on the interference score, indicating that in our study, the stressor did not change interference control in the overall sample. This was surprising, because other studies reported impaired inhibitory performance under stress (Sanger et al., 2014; Roos et al., 2017), and meta-analytical findings, although based on a small number of studies, suggested that the negative effect of acute stress on interference control is independent of stress severity and stress type (Shields et al., 2016). As our stress reactivity analysis revealed, the stressor elicited significant increases in all measured physiological and psychological indices of stress reactivity. Nevertheless, participants' ratings of anxiety after the baseline Stroop task, and the Stroop task under stress, did not differ significantly (cp. **Figure 3**). Studies showed that impairments in Stroop performance under stress can largely be attributed to subjective stress perceptions (Henderson et al., 2012). However, other studies also found associations of HPA axis and ANS reactivity with impaired inhibitory control (Sanger et al., 2014; Roos et al., 2017). As our study did not include a control condition without stress, we were not able to fully control for the influence of potential practice effects on the results. Participants might have performed better under stress because an assessment of inhibitory control without stress took place beforehand (see limitations). In conclusion, it remains unclear why the stressor failed to elicit the expected decline in behavioral interference control, and more studies on the effect of stress on executive functioning, and on the potential role of exercise, are necessary.

Associations With DLPFC Oxygenation

Along with behavioral parameters, DLPFC oxygenation was measured to account for neurophysiological mechanisms underlying interference control. Recent fNIRS studies demonstrated that more left-lateralized DLPFC oxygenation was associated with higher interference control (Zhang et al., 2014; Ludyga et al., 2019a). This effect has been attributed to differences in left and right DLPFC activation when stimulus conflict is anticipated and up-regulation of the attentional set is required (Vanderhasselt et al., 2009). According to lateralized Stroop studies, interference effects might be greater in the left hemisphere because, compared to the right hemisphere, the left hemisphere presents an overall advantage on most verbal tasks (Belanger and Cimino, 2002). Moreover, research with fNIRS showed that positive effects of exercise on interference control might be mediated by DLPFC lateralization. In 25 young adults, Byun et al. (2014) observed improved performance in a Stroop color-word matching task after a 10min bout of mild ergometer exercise, which was accompanied by pronounced activation of the left DLPFC in relation to Stroop interference. In a sample of 60 older adults, Hyodo et al. (2016) reported correlations between higher aerobic fitness and better Stroop performance, and mediation analysis revealed that this relationship was mediated by more left-lateralized DLPFC activation. In a recent study utilizing a combined fNIRS-EEG approach, our research group investigated mechanisms underlying the association between aerobic fitness and interference control in a sample similar to the present study (Ludyga et al., 2019a). While both left-lateralized DLPFC oxygenation, and greater N450 negativity, were associated with better Stroop performance, only N450 negativity mediated the fitness-interference control relationship. Again, no studies are available that investigated associations between exercise and interference control in the presence of acute psychosocial stress, and the present study provides first insights into this relationship. Overall, our data indicate a tendency toward left-lateralized activation in both groups and in both conditions (cp. **Figure 5**). No systematic differences in DLPFC oxygenation occurred between both groups and conditions. These results match our findings with regard to behavioral interference control, but provide no support for our hypothesis of increased left-lateralized DLPFC activity in the exercise group. From other studies we know that exercise improves interference control via facilitation of DLPFC activation (e.g. Yanagisawa et al., 2010; Byun et al., 2014), and that acute stress affects the PFC (Arnsten, 2009). While our study only assessed stress effects on activation and functioning of the DLPFC, our results do not allow conclusions on the activation of other PFC regions under stress, and potential corresponding effects of acute exercise.

Exercise Effects on Stress Reactivity

In our study, we observed that the acute exercise group showed lower stress reactivity than the control group in the parameters alpha-amylase and anxiety, but not in the parameters cortisol and heart rate. While these group differences in stress reactivity were not related to significant changes in interference control, they are relevant for different reasons. As research shows, the phase of adolescence, compared to other age groups, is characterized by a typical increase in stress reactivity in response to acute psychosocial stressors (Lupien et al., 2009; Stroud et al., 2009). The combination of frequent stress exposure in this age group (American Psychological Association, 2014) and potentially high stress reactivity, increases the risk of corresponding future stress-related health issues (Redmond et al., 2013; Turner et al., 2020). Therefore, a reduction in stress reactivity in the face of psychosocial stressors is often desirable. Our results now show that acute exercise has such potentially health-beneficial effects on stress reactivity.

Changes in stress reactivity in relation to exercise have been observed before, and are often explained with habituation effects of the stress response systems when exposed to regular exercise (Herman et al., 2005; Hackney, 2006), which then transfer to the reaction to psychosocial stressors (Sothmann, 2006). While this has often been demonstrated for regular exercise (Mücke et al., 2018), only few studies investigated such effects after a single exercise bout. Three relatively recent studies investigated the effects of acute exercise on physiological stress reactivity in young adults (Zschucke et al., 2015; Wood et al., 2018; Wunsch et al., 2019). Interestingly, although these studies differed largely with regard to exercise type (walking vs. bicycle ergometer vs. treadmill), exercise intensity (moderate walking vs. 70% of their individual maximum load vs. 60—70% of maximum oxygen uptake), time delay from exercise to stressor (30 min vs. 10 min vs. 90 min delay), stress task (TSST-G vs. Montreal Imaging Stress Task), and control task (passive control vs. light stretching), they consistently reported attenuated cortisol and/or alpha-amylase reactivity in the exercise group, compared to the control group. This initial data demonstrates that the effects of acute exercise on stress reactivity seem to be fairly robust and are related to a wide range of exercise modalities. In our slightly younger sample of male adolescents, and with exercise parameters within the range of these previous studies, we show similar results with regard to alpha-amylase, which represents stress reactions of the autonomic nervous system (Nater and Rohleder, 2009). However, no such effects were observed with regard to cortisol. Different effects of the exercise session on these parameters are unlikely to be the explanation for this result, as directly after the exercise or control condition, alpha-amylase as well as cortisol levels did not differ between groups. Studies have already shown that the reactions of HPA axis and ANS system to psychosocial stressors can be dissociated (Schommer et al., 2003). However, in this particular case, the reasons for these differences remain unclear. Lastly, our study indicated transient effects of exercise on self-reported anxiety. In response to the stressor, we observed lower increases in anxiety in the exercise group, compared to the control group. After the stressor, both groups reported similar anxiety levels. As other studies so far focused on physiological stress parameters, there is a lack of research on acute exercise effects on psychological stress reactivity, and our findings provide initial support for improved coping with stressors that are characterized by uncontrollability and socio-evaluative threat after an acute bout of exercise. Further studies are necessary to confirm these initial results.

Limitations

The results of our randomized, controlled examination have some limitations that need to be considered. As our sample consisted of healthy, male, right-handed adolescents with a rather high educational status, conclusions on other target groups need to be treated with caution. Further research with female participants, different age groups and educational status, or with clinical samples is necessary and could lead to different results. Furthermore, it is possible that different exercise conditions might have changed the results. It is noteworthy that in our study, a modified version of the TSST was used. The mental arithmetic task, as described in the original version by Kirschbaum et al. (1993), was replaced by a Stroop task in order to measure participants' interference control under the direct influence of the psychosocial stressor. Although both mental arithmetic and Stroop tasks have been used as stressors before (Dickerson and Kemeny, 2004), and substantial differences in stress reactivity are therefore unlikely, direct comparisons of our results with other TSST studies are limited. In our study, an acute exercise group was compared to an active control group. However, both groups underwent the complete stressor task, and no "no-stress" control group was present. Therefore, our study did not control for the effects of repeated Stroop task exposure, and our results may be confounded by practice effects. However, other studies reported no such effects after repeated Stroop task administration (Browne et al., 2016), and since it would have affected both groups equally, a change of the general patterns of results because of practice effects is unlikely. Finally, despite its advantages in the assessment of cortical brain activity (Zhang et al., 2014), the use of fNIRS has some limitations. It has been shown that fNIRS measurements can be partially affected by skin blood flow and systemic effects (Tachtsidis and Scholkmann, 2016). However, we expect the effect of such artifacts to be small in our analyses, because all Stroop tasks in our study were conducted under standardized conditions (the participants were instructed to remain seated, to avoid speaking and to breathe regularly throughout the measurement to keep these parameters constant). Moreover, because we calculated Stroop interference related to DLPFC activation as the difference between incompatible and compatible trials, the shared potential global artifacts of both trial types should cancel each other out (Hyodo et al., 2016).

CONCLUSION

Adolescents performing an acute exercise bout appear to show lower stress reactivity of the autonomic nervous system, and a lower increase in anxiety in response to a psychosocial stressor than their non-exercising peers. In contrast, a single exercise session does not seem to influence stress-induced changes in interference control and associated DLPFC oxygenation. Thus, such an exercise paradigm may only be valuable in buffering the autonomous stress response.

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 Ethikkommission Nordwest- und Zentralschweiz, Switzerland. Written informed consent was obtained from all participants. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MM, SL, and MG were responsible for the conceptualization and study methodology. SL contributed to the Software. MM, SL, and FC contributed to the formal analysis. MM was responsible for the investigation. UP and MG contributed to the resources. MM contributed to the writing of the manuscript (original draft). SL, FC, UP, and MG contributed to the writing of the manuscript (review and editing). UP and MG were responsible for the project supervision. MM was responsible for the project administration. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.581965/full#supplementary-material

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Associations Between Physical Fitness and Brain Structure in Young Adulthood

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A comprehensive analysis of associations between physical fitness and brain structure in young adulthood is lacking, and further, it is unclear the degree to which associations between physical fitness and brain health can be attributed to a common genetic pathway or to environmental factors that jointly influences physical fitness and brain health. This study examined genotype-confirmed monozygotic and dizygotic twins, along with non-twin full-siblings to estimate the contribution of genetic and environmental factors to variation within, and covariation between, physical fitness and brain structure. Participants were 1,065 young adults between the ages of 22 and 36 from open-access Young Adult Human Connectome Project (YA-HCP). Physical fitness was assessed by submaximal endurance (2-min walk test), grip strength, and body mass index. Brain structure was assessed using magnetic resonance imaging on a Siemens 3T customized ‘Connectome Skyra’ at Washington University in St. Louis, using a 32-channel Siemens head coil. Acquired T1-weighted images provided measures of cortical surface area and thickness, and subcortical volume following processing by the YA-HCP structural FreeSurfer pipeline. Diffusion weighted imaging was acquired to assess white matter tract integrity, as measured by fractional anisotropy, following processing by the YA-HCP diffusion pipeline and tensor fit. Following correction for multiple testing, body mass index was negatively associated with fractional anisotropy in various white matter regions of interest (all $|z|$ statistics $>$ 3.9) and positively associated with cortical thickness within the right superior parietal lobe (z statistic = 4.6). Performance-based measures of fitness (i.e., endurance and grip strength) were not associated with any structural neuroimaging markers. Behavioral genetic analysis suggested that heritability of white matter integrity varied by region, but consistently explained >50% of the phenotypic variation. Heritability of right superior parietal thickness was large (~75% variation). Heritability of body mass index was also fairly large (~60% variation). Generally, $\frac{1}{2}$ to $\frac{2}{3}$ of the correlation between brain structure and body mass index could be attributed to heritability effects. Overall, this study suggests that greater body mass index is associated with lower white matter integrity, which may be due to common genetic effects that impact body composition and white matter integrity.

Keywords: heritability, environment, gray matter structure, white matter integrity, physical fitness, body composition

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INTRODUCTION

Associations between performance-based physical fitness and neuroimaging markers of brain health have been studied fairly extensively in the context of aging, and to a somewhat lesser extent in the context of childhood development. Previous studies have shown that physical fitness—most commonly cardiorespiratory fitness—positively correlates with gray matter (GM) thickness or volume in various regions of the cortex in children and older adults (Gordon et al., 2008; Chaddock-Heyman et al., 2015; Wood et al., 2016; Williams et al., 2017; Esteban-Cornejo et al., 2019; Cadenas-Sanchez et al., 2020) and with hippocampal volume in older adults (Erickson et al., 2009; Cole et al., 2020). Other research has shown associations between physical fitness—again typically cardiorespiratory fitness—and higher diffusion-based white matter (WM) integrity (Marks et al., 2011; Tseng et al., 2013; Oberlin et al., 2015; Ding et al., 2018) or reduced lesion volume in older adults (Sexton et al., 2016). In children, one study found a weak association between upper-body strength and WM integrity in the frontal lobe (Rodriguez-Ayllon et al., 2020).

Relatedly, other research has looked at associations between body composition—most commonly body mass index (BMI)—and neuroimaging markers of brain health in youth and older adults. Higher BMI has been associated with smaller GM volume in various cortical and subcortical regions in adolescence (Kennedy et al., 2016) and late adulthood (Ho et al., 2011), with reduced WM volume in adolescence (Kennedy et al., 2016), and with lower cerebral WM integrity in older adults (Marks et al., 2011). Still other studies have examined large age spans ranging from very early adulthood into older age. These studies, too, have found that BMI negatively correlated with WM integrity, especially in midbrain and brain stem tracts (Verstynen et al., 2012) and subregions of the corpus callosum (Stanek et al., 2011). Altogether, these findings have been used to argue that improving physical fitness and body composition might improve brain health, and in turn, promote cognitive performance during development (Chaddock-Heyman et al., 2015) and reduce cognitive impairment during aging (Erickson et al., 2014).

Analysis of links between physical fitness and body composition with neuroimaging markers of brain health specifically in early adulthood has been somewhat overlooked, despite acknowledgment that a lifespan perspective on brain health is warranted, in which risk factors for deterioration in brain health are potentially present across the lifespan (Moffitt et al., 2016; Williamson et al., 2018; Tucker-Drob, 2019). Evidence for such associations could provide the grounds for future research that explores whether intervening in young adulthood to promote fitness and body composition might alter long-term trajectories of brain health into older age.

The Young Adult Human Connectome Project (YA-HCP) is a large neuroimaging study of approximately 1200 women and men aged 22 to 36 (Van Essen et al., 2013), which offers an excellent data source for exploring links between physical fitness and body composition with various neuroimaging markers of brain health. Beyond collecting high-quality multi-model neuroimaging data, the YA-HCP collects behavioral data in a variety of domains, including physical fitness and body composition (Barch et al., 2013). Previous studies using the YA-HCP have observed that higher BMI and lower submaximal cardiovascular endurance are associated with lower integrity within several WM tracts (Repple et al., 2018; Opel et al., 2019). Other YA-HCP analyses have shown that BMI correlates with cortical thickness, with the direction (negative versus positive) depending on the region and hemisphere (Vainik et al., 2018). In a recent study using the YA-HCP, we failed to observe an association between cortical thickness and either submaximal cardiovascular endurance or grip strength (Best, 2020). Like other studies in the field, our previous study was limited by focusing on only one type of brain structure (specifically, cortical thickness), despite knowledge that GM structure is distinct from WM structure, and even that cortical thickness is genetically and phenotypically distinct from cortical area (Winkler et al., 2010). As such, it is plausible that fitness and body composition might have different associations with different structural features of the brain. Further, although our previous study adjusted for participant height and weight in the regression analyses, BMI was not considered as an important predictor in its own right, and it is possible for fitness and body composition to have unique associations with brain structure.

Thus, the current study is motivated in part by the need for a comprehensive analysis involving multiple aspects of physical fitness and body composition along with various structural measures of brain health within a single sample with sufficient sample size to appropriately correct for multiple testing while maintaining reasonable statistical power. Using data from the YA-HCP, the current study estimated associations between submaximal cardiovascular endurance, grip strength, and BMI with cortical GM thickness and area, with subcortical GM volume, and with WM fractional anisotropy (FA), a commonly-used measure of WM integrity based on the flow of water molecules along WM tracts (Pierpaoli et al., 1996). Importantly, the default assumption made in most previous investigations is that associations between fitness/body composition and brain structure is linear across the range of scores; however, this may not necessarily be the case. Erickson et al. (2010) observed that the strongest association between physical activity and GM volume in older adults was at the highest quartile of physical activity, suggesting that a relatively large volume of physical activity might be necessary for detection of effects on brain structure. Whether such non-linear associations are observed for physical fitness or body composition is unknown, but the relatively large sample and wide distribution of fitness and body composition in the YA-HCP offers an opportunity to explore this possibility.

Assuming that links between physical fitness and brain structure exist in young adulthood, an important next step is to better understand the degree to which covariation in physical fitness and brain structure might be attributed to genetic versus environmental variation. The YA-HCP is well-suited to enhance such understanding because of its inclusion of genotype-confirmed monozygotic and dizygotic twin pairs, along with full-sibling non-twin pairs. Assuming that genetic overlap approximates 100% in monozygotic twins and 50% in dizygotic and non-twin pairs, behavioral genetic analyses can be conducted to estimate the heritability and environmental contributions to variation in fitness and brain structure, as well as the covariation between the two (Grasby et al., 2017). Previous research has found a moderate heritability contribution to the correlation between cardiovascular endurance and executive function (Best, 2020) and between BMI and executive function, cortical thickness and medial temporal lobe volume (Vainik et al., 2018). Research in other samples has shown a moderate heritability contribution to the BMI-executive function correlation in youth (Wood et al., 2019) and a more modest heritability contribution to the cardiovascular fitness-intelligence association among young men enlisted for military service (Aberg et al., 2009). Altogether, these studies suggest at least a modest genetic component to correlations between physical fitness and body composition, on the one hand, and neuro-cognition, on the other. To follow-up on our primary analyses, the current study conducted a set of behavioral genetic analyses among a subset of twin and full-sibling, non-twin pairs involved in the YA-HCP to estimate the degree to which genetics and the environment underpin associations identified in the larger sample.

MATERIALS AND METHODS

Study Design and Participants

Participant data were provided by the open-access YA-HCP 1200 Subjects Data Release (Van Essen et al., 2013). For our primary analyses with the entire sample, 1,113 participants had valid FreeSurfer-processed 3T structural MRI data and 1,065 participants had valid FSL-processed diffusion imaging of WM data. For behavioral genetic analyses, a subset of the entire sample was used, which entailed twin or full-sibling, non-twin pairs who participated in the study. Twin zygosity was verified by genotyping. Full-sibling, non-twin pairs were identified by having identical mother and father identification numbers, but not being twins. Full-siblings with an age discrepancy ≥5 years were excluded from behavioral genetic analyses.[1] For behavioral genetic analyses involving WM FA values, data from 134 monozygotic twin pairs, 72 dizygotic twin pairs, and 290 full-sibling, non-twin pairs were available. For behavioral genetic analyses involving GM, data from 138 monozygotic twin pairs, 78 dizygotic twin pairs, and 313 full-sibling, non-twin pairs were used.

Participants were healthy adults within the age range of 22–36, who were drawn primarily from families that included twins in Missouri, United States. Families were excluded where individuals within the family had severe neurodevelopmental disorders (e.g., autism), neuropsychiatric disorders (e.g., schizophrenia) or neurological disorders (e.g., Parkinson's disease). Individuals were also excluded if they had illnesses thought to impact neuroimaging data quality (e.g., high blood pressure or diabetes). Additional details on the participants and study design can be found elsewhere (Van Essen et al., 2013). Extensive details on all the measures included in the YA-HCP study can be found at: https://wiki.humanconnectome.org. The original study was approved by the Washington University Institutional Review Board. All participants provided written informed consent. Approval for this secondary analysis was provided by the Institutional Review Board at Simon Fraser University (Title: "Genetic Contributions to Cognition and Physical Functioning in Young Adults: Analysis of the Human Connectome Project Study"; Study no: 2019s0471).

Measures

Demographic and Other Covariate Variables

Age in years, gender, race/ethnicity, years of completed education, and annual total household income were self-reported. Gait speed (meters per second) was assessed over 4-meters, starting from rest, and was included to account for variance in the endurance measure due to differences in gait.

Physical Fitness

Two physical fitness measures from the NIH Toolbox for Assessment of Neurological and Behavioral Function ('NIH toolbox') were completed on the first of the 2-day assessment schedule. The NIH toolbox includes psychometrically-validated measures of cognition and behavior, suitable for use across the human lifespan (Gershon et al., 2013;Weintraub et al., 2013). Details on its implementation within the YA-HCP can be found elsewhere (Barch et al., 2013).

Sub-maximal cardiovascular endurance was assessed by having participants walk as far as possible over a 2-min period of time, back-and-forth over a 50-ft course. The total distance is recorded. Two trials were completed, with the trial with the longer distance walked used as the outcome of interest. Full force grip strength was measured with both hands using a Jamar Plus Digital dynamometer with the elbow bent to 90 degrees and arm against the trunk. Practice was conducted for each hand. Pounds of force for the dominant hand was used as the outcome of interest. Both fitness measures have shown good test–retest reliability (Intraclass correlation coefficient [ICC] ≥0.88) and convergent validity ($r \geq 0.77$) with 'gold standard' measures of endurance and grip strength across adulthood (Reuben et al., 2013). Further, although grip strength is a more direct measure of upper body strength, it also strongly correlates with knee extension performance ($r \geq 0.77$), a measure of lower body strength, suggesting grip strength may serve as a proxy for body strength more generally (Bohannon et al., 2012). Height was reported in inches and weight was reported in pounds; these values were converted to BMI with the following formula: $BMI = 703 \times \frac{weight(lbs)}{height(in)^2}$. Using the guidelines from the United States Centers for Disease Control and Prevention[2], a BMI below 18.5 indicates underweight, 18.5 to 24.9 indicates normal or health weight, 25 to 29.9 indicates overweight, and 30 and above indicates an obese weight status.

[1] It was possible for a given individual to be included in multiple sibling pairs, as there were families with up to six full siblings. In such instances, values were averaged across all pairs of the same type (i.e., DZ, MZ, non-twin full-sibling types) in which the given individual was involved, so as to avoid double-counting individuals. The vast majority of these involved non-twin, full-sibling pairs.

[2] www.cdc.gov

Structural MRI Data Acquisition and Processing

Gray matter imaging acquisition and processing was conducted by the YA-HCP research team with no additional processing on the freely-available data. Extensive details on the imaging protocol are found elsewhere, including details of additional scanning paradigms not included in the current study (Van Essen et al., 2012, 2013). All participants were scanned on a Siemens 3T customized 'Connectome Skyra' at Washington University in St. Louis, using a 32-channel Siemens head coil. Two T1-weighted and two T2-weighted scans were acquired at a spatial resolution of 0.7 mm isotropic voxels over two sessions. Each scan was evaluated by a trained rater for overall quality and only good/excellent scans were submitted to the structural pipelines, which used FreeSurfer 5.1 software and custom steps that combine the T1- and T2-weighted images for more accurate delineation of white and pial surfaces (Van Essen et al., 2013). Initial registration to MNI152 space was completed by FSL's FLIRT tool, followed by non-linear FNIRT to align subcortical structures. Cortical surface alignment was achieved using a surface-based registration using FreeSurfer, separately for each hemisphere. Average cortical thickness and surface area was obtained in 68 regions of interest (ROIs) across the two hemispheres. Additionally, subcortical GM volume was obtained in 14 ROIs in the limbic system.

Diffusion images were acquired at a spatial resolution of 1.25 mm isotropic voxels during a session including six runs (each 9 min 50 s in duration). Initial pre-processing of diffusion data was conducted by the YA-HCP research team and included intensity normalization across runs, 'TOPUP' susceptibility-induced distortion correction, and 'EDDY' eddy current and motion correction (Glasser et al., 2013). Subsequent processing was conducted by the current research team using standard tract-based spatial statistics in FSL (Smith et al., 2006). Fractional anisotropy (FA) images were registered to the FMRIB58 FA template and averaged to create a mean FA image. This image was used to create a WM skeleton using an FA threshold of 0.2. The Johns Hopkins University ICBM-DTI-81 WM atlas (Mori et al., 2008; Oishi et al., 2008), which consists of 48 ROIs, was used to mask the WM skeleton and average FA values for every ROI was obtained per participant.

Statistical Analyses

Analyses were conducted using R version 4.0.2[3] using the Rstudio environment[4]). An *a priori* power calculation was not conducted given that this is a secondary analysis of an existing dataset. For each analysis the maximum sample size possible was used. The first step was to regress the cortical thickness and surface area values, subcortical volumes and WM FA values on a set of covariates (age, gender, ethnicity, income, education, gait speed, and intracranial volume) and the physical fitness measures (grip strength, submaximal endurance, and BMI). All fitness measures were included together in the same regression model so as to model their independent associations with the neuroimaging outcomes. Generalized linear models fit by restricted estimated maximum likelihood were used for these regressions. To allow for non-linearity in the association of age and physical fitness with the outcome of interest, restricted cubic splines were specified with knots located at the 10th, 50th, and 90th percentile values of the age and physical fitness variables (Harrell, 2019a). A compound symmetry covariance matrix accounted for the clustering of participants by maternal ID (i.e., twin and non-twin siblings are not independent participants). A separate model was constructed for each outcome. All predictors were retained in the models regardless of the statistical significance of their Wald test. These regression models were constructed using rms version 6.0.1 (Harrell, 2019b). Control of the type I error rate was achieved by first allocating an equal portion of an overall $\alpha = 0.05$ to each of the four outcome domains (i.e., cortical thickness and area, subcortical volume, and WM FA) and then to each of the three key predictors (endurance, strength, and BMI). Next, because outcomes were anticipated to correlate with one another (i.e., thickness in one region correlates with thickness in another region), the effective number of independent tests within each outcome domain was calculated using an approach that accounts for the degree of covariation among outcomes within the same domain (Nyholt, 2004). Thus, the α for the test of a specific predictor and region within a domain was calculated as:

$$\alpha_{corrected} = \frac{0.05}{4 \times 3 \times tests_{independent}},$$

where the estimated number of independent tests was 40.6, 57.8, 52.4, and 10.3 for FA, cortical thickness, cortical area, and subcortical volume measures, respectively. These corrected two-sided α values translated into a z statistic threshold of 3.88 for the FA outcomes, 3.97 for cortical thickness outcomes, 3.95 for cortical area outcomes, and of 3.54 for the subcortical volumes.

The second step was to estimate the proportion of phenotypic covariance between neuroimaging measures and physical fitness that can be attributed to heritability versus environmental sources. These analyses were limited to monozygotic twin, dizygotic twin, and full-sibling non-twin pairs with an age discrepancy of less than 5 years. Using the package OpenMx (version 2.17.4), a bivariate Cholesky decomposition twin model was constructed (Grasby et al., 2017). The Cholesky decomposition models specified that phenotypic variation in neuroimaging and physical fitness could be attributed to heritability variance (A), shared environmental variance (C), a twin-specific shared environment (T), and non-shared environmental variance (E) (**Figure 1**). These sources of variation are estimated by assuming that monozygotic twins share 100% of heritability effects and that dizygotic twins and full-sibling non-twins each share 50% of heritability effects. The shared environmental effects are equivalent for all three groups; additionally, monozygotic and dizygotic twins have another shared environmental effect that non-twins do not have. To estimate the heritability and environmental

[3] r-project.org
[4] Rstudio.com

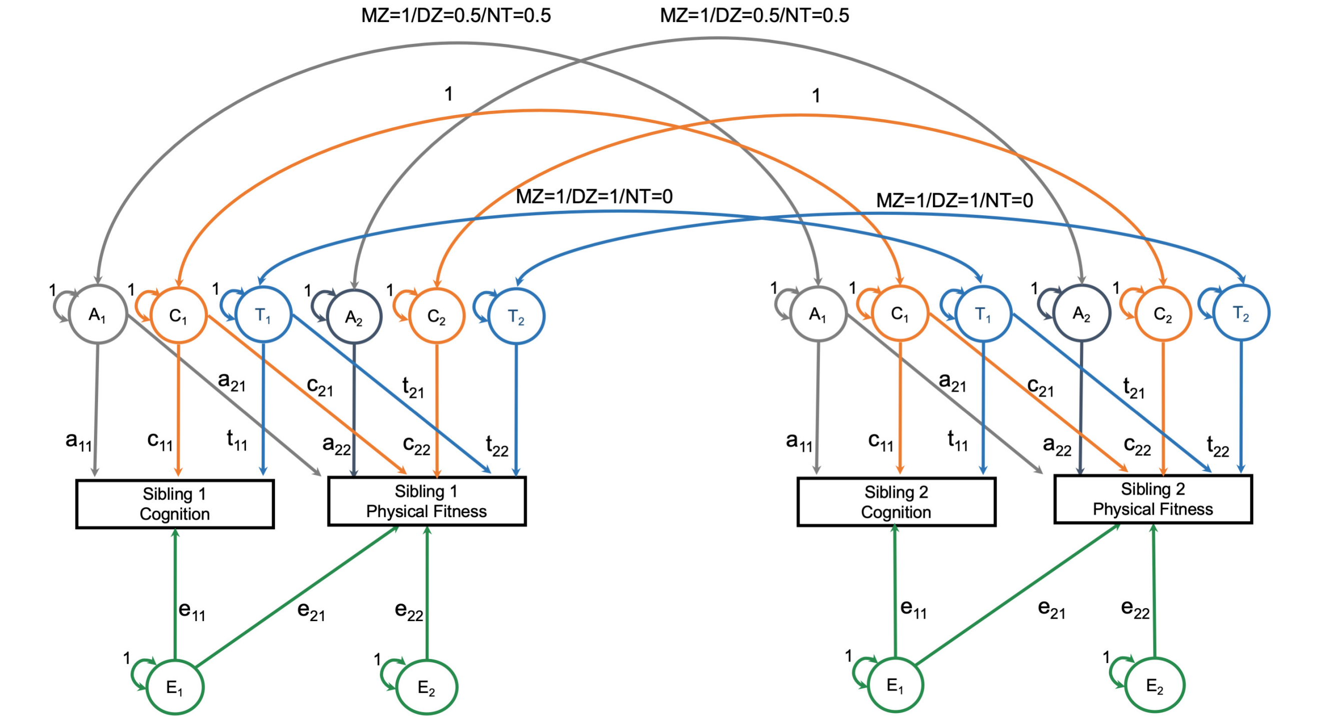

FIGURE 1 | Overview of bivariate Cholesky decomposition model.

contributions to the correlation between neuroimaging and physical fitness, the observed physical fitness variable is also allowed to load onto the latent heritability and environmental (shared, twin-specific, and non-shared) contributors to neuroimaging variation (Grasby et al., 2017). The result is the estimation of the variation in neuroimaging and physical fitness, as well as the covariation between neuroimaging and physical fitness. Prior to being entered into the Cholesky decomposition, neuroimaging and physical fitness variables were regressed on age (with non-linear restricted cubic spline effects), sex, race, education, annual income, and the interaction between age and sex in an ordinary least squares regression model (one model per outcome including all twins together).

The assumptions of equality of means and variances across twin order and zygosity were tested using the likelihood ratio test of nested models. A saturated model was fit first, in which all means and variances were allowed to vary freely across twins and zygosity. Next, means and variances were constrained to be equal across twin order, and then, across zygosity. Finally, the ACTwE model was estimated. To summarize the results of this model, standardize estimates and standard errors for each of the labeled paths in **Figure 1** (e.g., "a11") are presented, as well as the proportion of variation of the cross-trait correlation that can be attributed to each of the components (i.e., A, C, Tw, or E). (Note. Total variance or covariance is the sum of the A, C, Tw, and E components. Covariance can then be converted into a correlation by dividing by the product of the standard deviation of the cognition measure and the standard deviation of the fitness measure).

All data used for the current study can be freely obtained by qualified registered researchers[5] and the complete R analysis script can be found at https://osf.io/ykcm6/.

RESULTS

Sample Characteristics and Initial Associations

Demographic and physical fitness data on the full sample (i.e., all participants with GM and WM neuroimaging data) are summarized in **Table 1**. Mean age was roughly 29 years and 46% were male. Nearly 70% of the sample was non-Hispanic white. Average BMI fell in the overweight range. Endurance, and to a lesser extent grip strength, were on average higher than the age-based population norms (mean = 100) on which these measures were validated.

Simple bivariate correlations among age and physical fitness measures are shown in **Table 2**. Although gait speed was not a primary measure of interest, it is included as well. Age only weakly correlated with the other measures; endurance was modestly correlated with gait speed, grip strength and BMI ($|r| \sim 0.2 - 0.4$).

[5] https://db.humanconnectome.org/

TABLE 1 | Descriptive information on total sample.

Variable	
Sample size	1065
Age, years [mean (*SD*)]	28.75 (3.67)
Sex, male (%)	490 (46.0)
Race/ethnicity (%)	
Asian or Pacific Islands	64 (6.0)
Black/African American	148 (13.9)
Hispanic/Latino	94 (8.8)
Non-Hispanic, White	734 (68.9)
Other	25 (2.3)
Annual household income (%)	
<$10k	72 (6.8)
10–20k	82 (7.7)
20–30k	136 (12.8)
30–40k	126 (11.9)
40–50k	106 (10.0)
50–75k	225 (21.2)
75-100k	146 (13.8)
≥100k	166 (15.7)
Years of education (%)	
11 or less	36 (3.4)
12	146 (13.7)
13	65 (6.1)
14	131 (12.3)
15	65 (6.1)
16	454 (42.7)
17 or more	167 (15.7)
Gait speed, meters per second [mean (*SD*)]	1.32 (0.20)
Body mass index [mean (*SD*)]	26.40 (5.11)
Endurance, age normed [mean (*SD*)]	108.07 (13.94)
Grip strength, age normed [mean (*SD*)]	103.56 (20.12)

TABLE 2 | Correlations among physical fitness measures and age.

	Age	Endurance	Strength	BMI	Gait
Age	1	−0.09	−0.09	0.09	0.04
Endurance		1	0.28	−0.35	0.24
Strength			1	0.15	−0.02
BMI				1	−0.09
Gait					1

Physical Fitness and Structural Neuroimaging Markers

White Matter Fractional Anisotropy

Twelve of the possible 48 WM ROIs were associated with BMI with *z* test statistic that exceeded the multiplicity-corrected threshold. These ROIs are summarized in **Table 3** and are arranged from largest to smallest |*z*| statistic. Identified regions included midbrain tracts (bilateral cerebral peduncle and pontine crossing), bilateral fornix and hippocampal portion of the cingulum, and left sagittal stratum, among others. In all cases, greater BMI was associated with lower FA values.

TABLE 3 | Summary of effects of body mass index on FA values.

White matter region of interest	Abbr.	Effect	*S.E.*	*Z* stat
Cerebral peduncle left	CpL	−0.0081	0.0011	−7.7
Fornix cres left	FcL	−0.01	0.0016	−6.5
Fornix cres right	FcR	−0.0092	0.0016	−5.9
Cerebral peduncle right	CpR	−0.0063	0.0011	−5.8
Pontine crossing tract	Pct	−0.0074	0.0015	−5
Sagittal stratum left	SsL	−0.0072	0.0015	−4.9
Cingulum hippocampus right	ChR	−0.0094	0.002	−4.7
Retrolenticular part internal capsule right	RpicR	−0.0062	0.0014	−4.4
Cingulum hippocampus left	ChL	−0.0082	0.0019	−4.3
Corticospinal tract left	CtL	−0.0073	0.0018	−4.1
Superior fronto-occipital fasciculus right	SffR	−0.0057	0.0015	−3.9
Inferior cerebellar peduncle right	IcpR	−0.0072	0.0018	−3.9

Abbr., abbreviation. S.E., standard error. Z stat, Z statistic.

Marginal plots of the association between BMI and these WM ROIs are shown in **Figure 2**, which account for the covariates and other fitness measures. In some instances, the association between BMI and FA was fairly constant across the range of BMI values (e.g., left and right fornix), whereas in other instances, the association appeared to dissipate somewhat with more extreme BMI values (e.g., left and right cerebral peduncle).

Neither endurance nor grip strength had associations with the WM ROIs with *z* statistics beyond the threshold. Comprehensive results for all WM ROIs can be found in Section "Comprehensive White Matter Fractional Anisotropy Results" for the **Supplementary Material**.

Gray Matter Structure

Body mass index was positively associated with right superior parietal thickness (see **Table 4**). As shown in the marginal plot in **Figure 3** this association was strongest as BMI increased from the normal to the overweight range and then weakened somewhat with more extreme BMI values. No additional fitness associations with GM structure (whether thickness, area, or subcortical volume) had significant *z* statistics. Comprehensive results for all GM ROIs can be found in Section "Comprehensive Gray Matter Results" for the **Supplementary Material**.

Bivariate Behavioral Genetic Analysis of Fitness and Brain Structure

Table 5 presents descriptive data for the demographic and physical fitness measures for each of the three sibling pair types, which shows similarities between participating siblings and among the three sibling pair types. Based on the results of the larger sample, bivariate genetic models were estimated between BMI and 12 WM ROIs and right superior parietal GM thickness. The full ACTwE model showed small estimates with large standard errors for the shared environmental and twin-specific environmental effects. As has been done in previous research (Vainik et al., 2018; Wood et al., 2019),

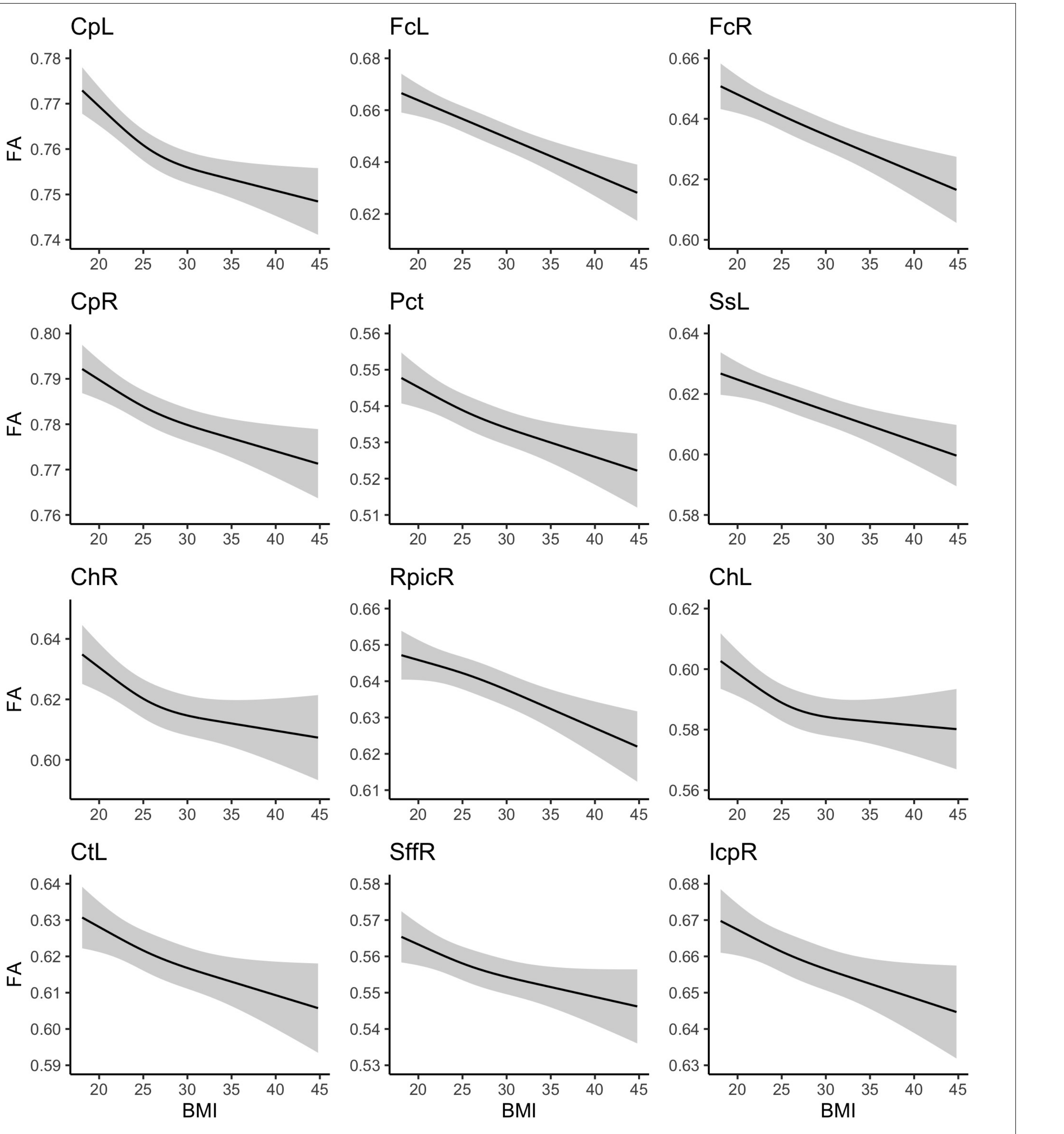

FIGURE 2 | Association between body mass index and white matter fractional anisotropy values.

the loadings and cross-loadings for these two effect were fixed to zero, resulting in a simpler AE bivariate model. Across brain regions, this simpler AE model did not result in a worsening in fit according to likelihood ratio tests (smallest likelihood ratio test *p*-value was 0.14 across the 12 WM and 1 GM ROIs), and therefore, is described below. Comparison between ACTwE and AE models and tests for the assumptions of equality of means and variances can be found in Section "Behavioral Genetic Model Comparisons" of the **Supplementary Material**, where we provide −2*log likelihood values, degrees of freedom, and Akaike Information Criterion for each model.

TABLE 4 | Summary of effects of body mass index on GM cortical thickness.

Outcome	Effect	*S.E.*	*Z* stat
R Superior parietal	0.022	0.0047	4.6

S.E., standard error. Z stat, Z statistic.

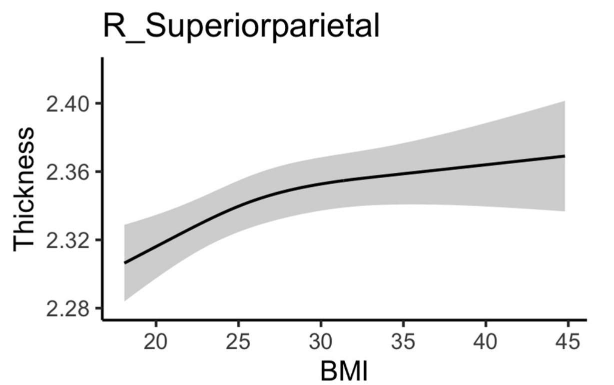

FIGURE 3 | Association between body mass index and gray matter thickness values.

White Matter Fractional Anisotropy

Initial bivariate correlations across siblings, across traits, and across siblings and traits for the three sibling pair types are shown in **Figure 4** for the 12 WM ROIs. These provide a helpful preview to the formal behavioral genetic analyses presented below. Body mass index was strongly correlated among MZ twins ($r \sim 0.61$), and was weakly correlated among DZ twins and non-twin siblings ($r \sim 0.20 - 0.27$). This suggests an important role of heritability in BMI variation. Similarly, WM FA was most strongly correlated within MZ twins for all 12 ROIs, also suggesting an important role of heritability for WM integrity. Whether DZ twins or non-twin siblings had the next strongest correlation varied by ROI, thereby suggesting inconsistency with regard to twin-specific versus a more general shared environmental effect. Cross-trait and cross-trait/cross-sib ('ct/cs' in **Figure 4**) correlations also varied somewhat depending on the WM ROI, though in general, the strongest negative correlation was among MZ twins and further, the cross-trait/cross-sibling correlation was

TABLE 5 | Descriptive information on each sibling pair type.

	Dizygotic twin pairs		Monozygotic twin pairs		Full, non-twin siblings	
	Sibling 1	**Sibling 2**	**Sibling 1**	**Sibling 2**	**Sibling 1**	**Sibling 2**
Age, years [mean (*SD*)]	29.2 (3.6)	29.2 (3.6)	29.3 (3.3)	29.3 (3.3)	28.6 (3.6)	28.9 (3.7)
Sex, male (%)	30 (39.0)	30 (39.0)	57 (41.3)	57 (41.3)	135 (43.4)	160 (51.4)
Race/ethnicity (%)						
Asian or Pacific Islands	2 (2.6)	2 (2.6)	6 (4.3)	5 (3.6)	15 (4.8)	19 (6.1)
Black/African American	10 (13.0)	10 (13.0)	12 (8.7)	12 (8.7)	44 (14.1)	44 (14.1)
Hispanic/Latino	0 (0.0)	0 (0.0)	6 (4.3)	5 (3.6)	37 (11.9)	35 (11.3)
Non-Hispanic, white	64 (83.1)	63 (81.8)	113 (81.9)	114 (82.6)	205 (65.9)	208 (66.9)
Other	1 (1.3)	2 (2.6)	1 (0.7)	2 (1.4)	10 (3.2)	5 (1.6)
Annual household income (%)						
<$10k	5 (6.5)	3 (3.9)	10 (7.2)	7 (5.1)	17 (5.5)	19 (6.1)
10–20k	3 (3.9)	11 (14.3)	4 (2.9)	17 (12.3)	35 (11.3)	11 (3.5)
20–30k	12 (15.6)	6 (7.8)	21 (15.2)	10 (7.2)	30 (9.6)	42 (13.5)
30–40k	11 (14.3)	7 (9.1)	9 (6.5)	20 (14.5)	34 (10.9)	40 (12.9)
40–50k	3 (3.9)	6 (7.8)	13 (9.4)	14 (10.1)	41 (13.2)	35 (11.3)
50–75k	26 (33.8)	22 (28.6)	26 (18.8)	29 (21.0)	63 (20.3)	63 (20.3)
75–100k	9 (11.7)	9 (11.7)	27 (19.6)	21 (15.2)	44 (14.1)	46 (14.8)
≥100k	8 (10.4)	13 (16.9)	28 (20.3)	20 (14.5)	47 (15.1)	55 (17.7)
Years of education (%)						
11 or less	4 (5.2)	1 (1.3)	4 (2.9)	7 (5.1)	8 (2.6)	14 (4.5)
12	8 (10.4)	9 (11.7)	21 (15.2)	19 (13.8)	36 (11.6)	31 (10.0)
13	3 (3.9)	4 (5.2)	10 (7.2)	7 (5.1)	21 (6.8)	19 (6.1)
14	10 (13.0)	9 (11.7)	14 (10.1)	15 (10.9)	40 (12.9)	39 (12.5)
15	2 (2.6)	8 (10.4)	5 (3.6)	9 (6.5)	24 (7.7)	18 (5.8)
16	33 (42.9)	37 (48.1)	61 (44.2)	53 (38.4)	133 (42.8)	136 (43.7)
17 or more	17 (22.1)	9 (11.7)	23 (16.7)	28 (20.3)	49 (15.8)	54 (17.4)
Gait speed, meters per second [mean (*SD*)]	1.3 (0.2)	1.3 (0.2)	1.4 (0.2)	1.3 (0.2)	1.3 (0.2)	1.3 (0.2)
Body mass index [mean (*SD*)]	26.6 (5.3)	26.4 (5.6)	26.3 (4.8)	26.0 (4.6)	26.6 (5.4)	26.6 (5.4)
Endurance, age normed [mean (*SD*)]	109.2 (13.0)	111.7 (10.3)	112.1 (11.2)	111.3 (13.5)	109.7 (12.1)	110.3 (11.9)
Grip strength, age normed [mean (*SD*)]	116.6 (9.7)	115.9 (11.2)	116.0 (10.9)	115.6 (10.4)	116.8 (11.7)	117.3 (11.9)

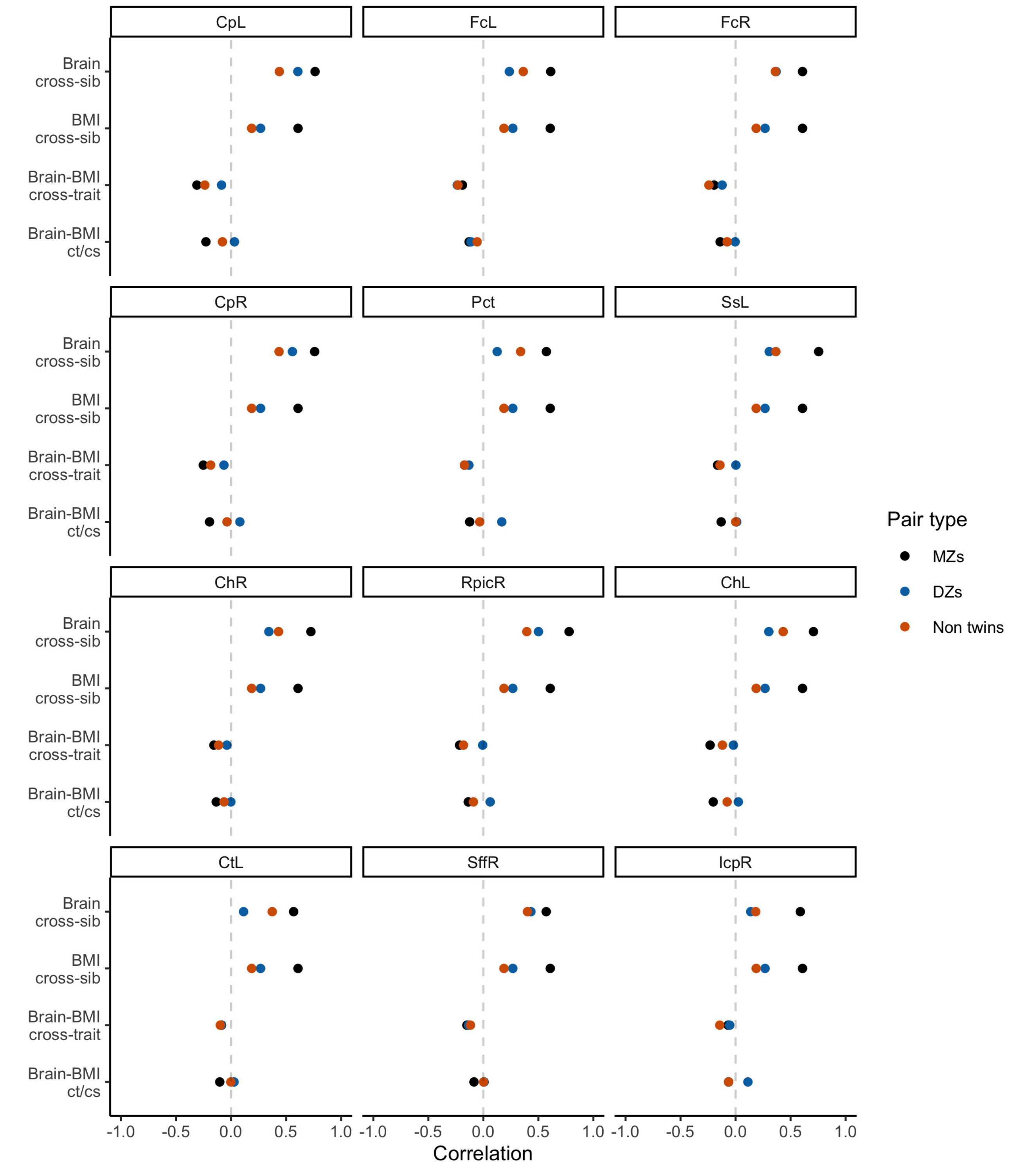

FIGURE 4 | Phenotypic correlations across siblings and across traits.

nearly as strong as the cross-trait correlation among MZ twins. This implies at least some role of heritability in the correlation between BMI and FA values; however, due to these correlations being generally quite modest (i.e., at most $r \sim -0.30$), the absolute role of heritability is also anticipated to be modest.

Standardized estimates and 95% confidence intervals for each of the paths in the bivariate Cholesky decomposition model are provided for each of the 12 WM ROIs in **Figure 5**. Following on the correlations described directly above, there were strong heritability loadings on WM FA variance (path a11) and BMI variance (a22). Similarly, there were strong, precisely estimated environmental effects for FA variance (e11) and BMI variance (e22). The point estimate for the genetic cross-loading (a21) was negative and modest ($\beta \sim -0.20$); in some instances, the confidence interval for this estimate crossed

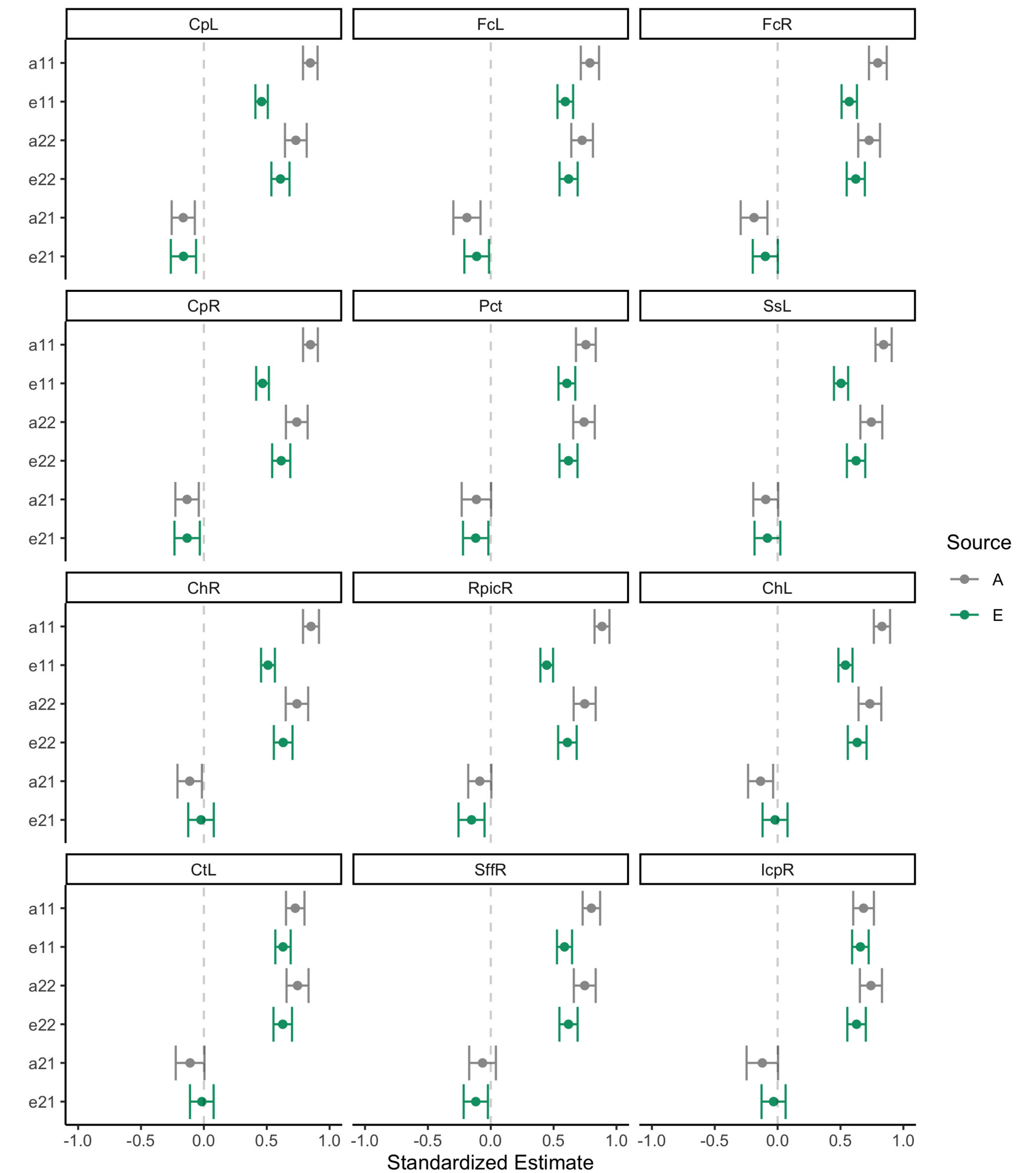

FIGURE 5 | Behavioral genetic path estimates for body mass index and white matter fractional anisotropy.

into positive numbers, suggesting some uncertainty about the nature of this effect. The point estimate for the environmental cross-loading (e21) was also quite small, generally smaller in magnitude than the genetic cross-loading. The confidence interval for this estimate was fairly narrow, but at times crossed into positive numbers.

These standardized estimates were then converted into variances and used to visualize how much of the variation in FA values and BMI could be attributed to each of the four sources. For example, in the AE model, WM FA variance is defined as below:

$$Var_{FA} = Var_{FA_A} + Var_{FA_E}$$

For WM FA, each of the variance components is the square of the respective standardized loading. For example,

$$Var_{FA_A} = a_{11}^2$$

For BMI, each of the variance components is the sum of the respective squared cross-loading and the squared endurance-specific standardized loading. For example,

$$Var_{BMI_A} = a_{21}^2 + a_{22}^2$$

The estimates from the AE model can also be used to partition the phenotypic correlation into A and E components. For example, the portion of the correlation attributed to heritability can be estimated by first estimating the covariance:

$$Cov_A = a_{11} \times a_{21}$$

And then converting that value into a correlation:

$$Cor_A = \frac{Cov_A}{(Var_{FA_A} + Var_{FA_E})^{\frac{1}{2}} \times (Var_{BMI_A} + Var_{BMI_E})^{\frac{1}{2}}}$$

Proportions of the variances and of correlations are plotted in **Figure 6**. The decomposition of BMI variance is roughly identical across models (as expected) and shows that heritability contributed to roughly 50% of variance. Similarly, heritability contributed to between 50 and 78% variance in WM FA, depending on the ROI. Environmental factors, by design, explained the remainder of the variance. Covariances were converted to correlations and are also shown in **Figure 6**. As expected, the total phenotypic correlation was modestly negative, ranging between −0.20 and −0.25. Generally, heritability accounted for $> \frac{1}{2}$ of this correlation. Section "White Matter Fractional Anisotropy" of the **Supplementary Material** shows the analysis of these 12 WM ROIs using the ACTwE model.

Gray Matter Structure

All of the above behavioral genetic analyses were repeated on the right superior parietal thickness, with the results summarized in **Figure 7**. As can be seen across the panels, there was a strong heritability effect for cortical thickness in addition to BMI (as described above). Analysis of the contributors to the correlation between BMI and cortical thickness in this region showed small positive effects for heritability (a21) and environment (e21) with confidence intervals that slightly cross into negative territory (see panel B). Heritability was estimated to contribute to 74% of variation of the variance in GM thickness and to slightly over $\frac{1}{2}$ of the small positive phenotypic correlation (panel C). Section "Gray Matter Structure" of the **Supplementary Material** shows the analysis of this GM ROI using the ACTwE model.

DISCUSSION

In this large study of young adults, we observed that BMI, but not performance-based measures of fitness, negatively correlated with WM integrity in various WM tracts. Except for a single positive association between BMI and cortical thickness in the right superior parietal lobe, we failed to observe associations between either physical fitness or BMI with cortical or subcortical GM structure. Along with a small set of previous studies (Aberg et al., 2009; Repple et al., 2018; Williamson et al., 2018; Opel et al., 2019; Repple et al., 2019), we bring attention to the fact that modifiable risk factors, such as BMI, correlate with brain health even in young adulthood. Our results support a lifespan perspective on neurocognitive aging, in which it may be fruitful to intervene many decades prior to the onset of cognitive impairment to effectively reduce negative impacts of cognitive aging (Moffitt et al., 2016; Tucker-Drob, 2019).

Body Composition and Neurocognitive Health

These results add to a growing literature associating high BMI and obesity with lower neurocognitive functioning and brain health at various points in the lifespan (Gunstad et al., 2007, 2008; Raji et al., 2010; Kennedy et al., 2016). As expected, our results confirm a previous study that included data from the YA-HCP that showed that high BMI was associated with widespread reduced WM integrity (Repple et al., 2018). The novelty of the current findings is that by also including several structural markers of GM, we observed a fairly selective association between BMI and WM integrity that does not extend to GM, with the single exception in the right superior parietal lobe. Also, by including upper-body strength and submaximal cardiovascular endurance as additional predictors of interest, we show that the effects of BMI cannot be explained by these performance-based fitness measures, and further, that these fitness measures were not uniquely associated with brain structure. Finally, by allowing for non-linearities in these associations, we observed that in instances in which the association deviated from linear, the most common pattern was for the slope to be steepest over the range of BMI values representing normal through overweight (i.e., 18–30), after which the slope became shallower. This was most apparent for WM in the bilateral cerebral peduncle and bilateral hippocampal portion of the cingulum, and for the right superior parietal GM thickness.

WM integrity begins to decline in mid adulthood and it correlates with cognitive performance; furthermore, loss of WM integrity and other WM abnormalities are features of various dementia subtypes, including Alzheimer's disease (Wassenaar et al., 2019). Our findings are consistent with previous studies showing that although there is a negative association between

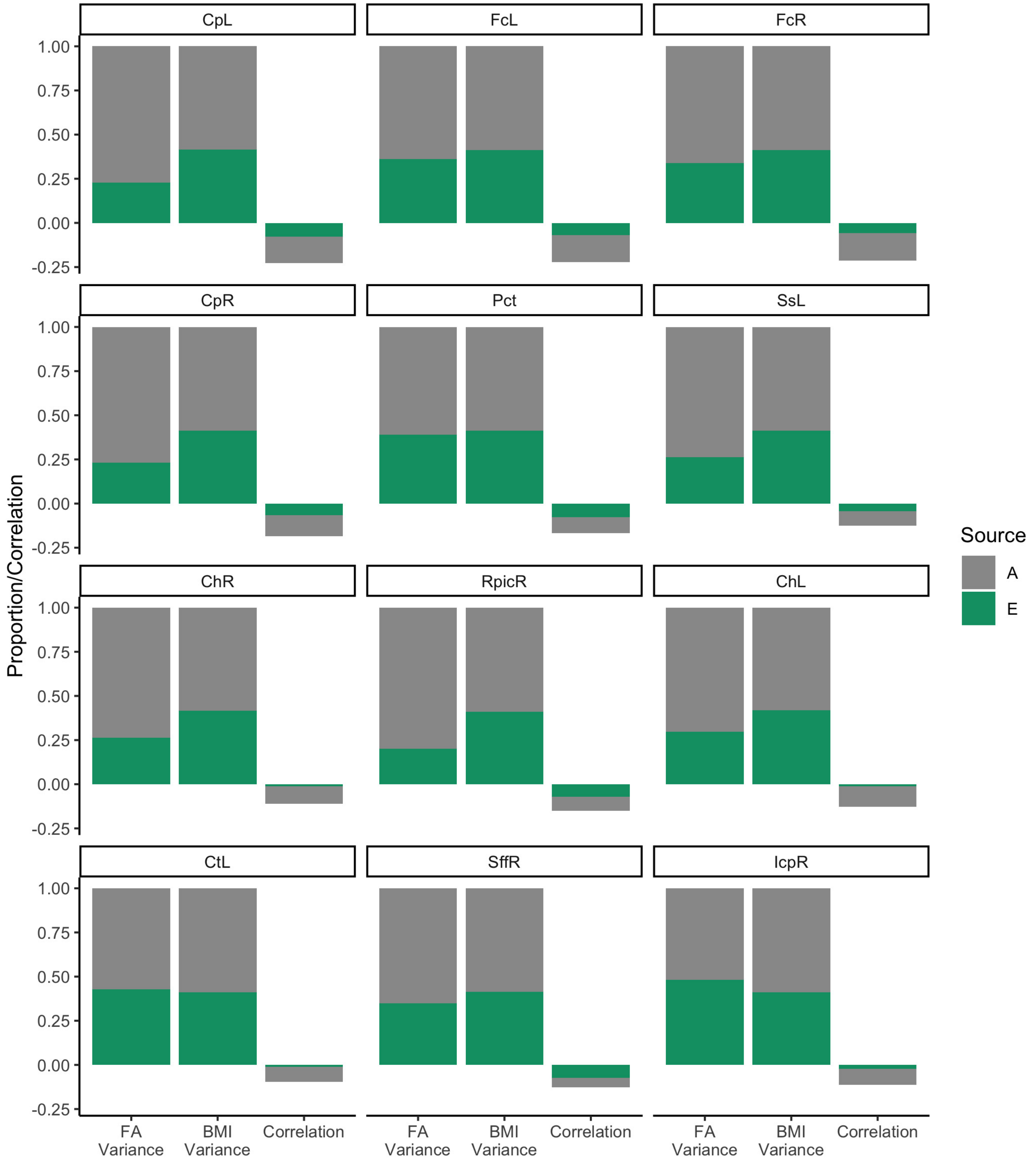

FIGURE 6 | Variance and correlation components for body mass index and white matter fractional anisotropy.

BMI and WM integrity throughout the brain, among the strongest statistical signals were subcortical brain stem pathways, including bilateral cerebral peduncle and pontine cross tract (Verstynen et al., 2012; Repple et al., 2018). By linking the midbrain to the thalamus, and to the cerebrum more generally, the cerebral peduncles are critically involved in motor and sensory functions, including motor control and coordination (Jane et al., 1968). Our findings also support previous studies showing a negative association between BMI and WM integrity in the fornix (Stanek et al., 2011; Xu et al., 2013). The fornix carries projection fibers from the hippocampus and is implicated in higher-order learning and memory (Kantarci, 2014). Decreased

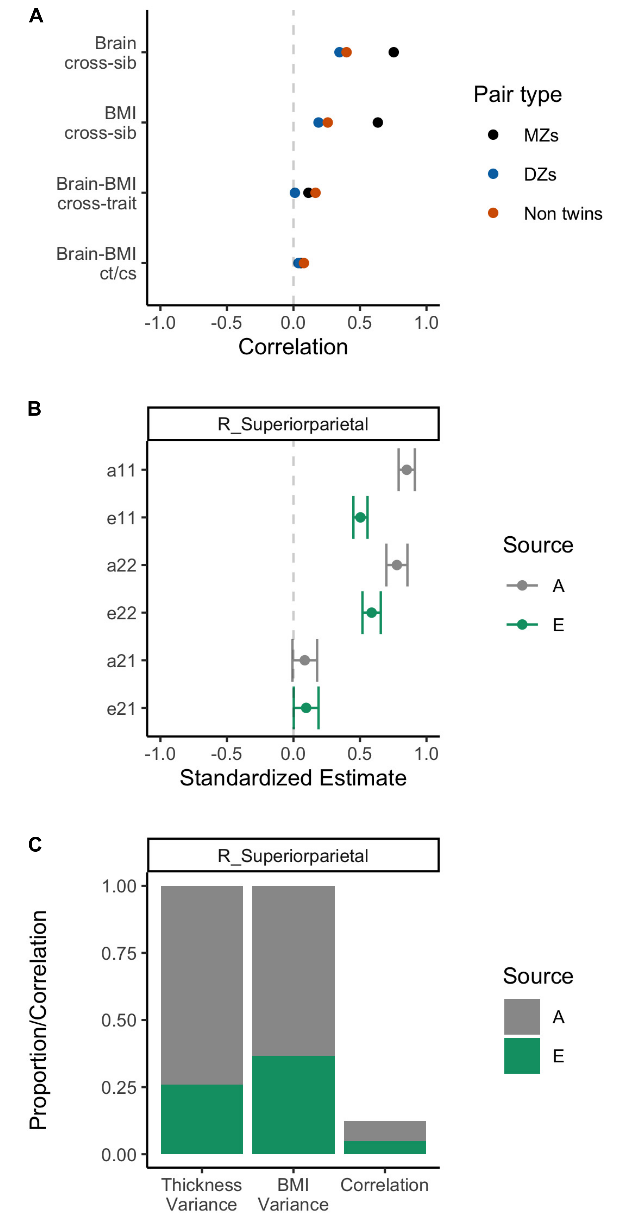

FIGURE 7 | Summary of behavioral genetic analyses of body mass index and right superior parietal thickness, including cross-sibling, cross trait correlations **(A)**, path estimates from AE bivariate model **(B)**, and variance and correlation components from AE bivariate model **(C)**.

fornix FA is observed with increasing age, and in mild cognitive impairment and Alzheimer's disease (Kantarci, 2014). We also observed the BMI-FA association in the bilateral hippocampal portion of the cingulum, which has also been linked to memory functioning (Ezzati et al., 2016) and to Alzheimer's disease (Dalboni Da Rocha et al., 2020). In light of the association of BMI in midlife with risk of dementia in late life (Kivimaki et al., 2018), it is possible that these WM tracts may play some role in transmitting this effect.

Similar to a previous analysis of YA-HCP data (Vainik et al., 2018), we observed a positive association between BMI and right superior parietal thickness; however, unlike this previous analysis, we failed to observe associations within other GM regions. Reasons for this discrepancy may include a stricter significance threshold in the current study that did not detect the weaker effects reported previously and the larger set of covariates used in the current study, which notably included performance-based physical fitness, educational attainment, and annual income.

We also failed to observe associations between either submaximal cardiovascular endurance or grip strength with any of the markers of brain structure, which is inconsistent with a previous analysis of the YA-HCP data that found an association between endurance and WM integrity (Opel et al., 2019). However, the current analysis differed in its analytic approach by including a larger set of covariates and using an ROI-based, as opposed to a voxel-based, approach to analyzing the associations between BMI and neuroimaging data. The lack of associations between fitness and brain structure is also inconsistent with other studies that have explored these associations in youth (Chaddock-Heyman et al., 2015) and older adults (Oberlin et al., 2015). The inconsistency with the current results could arise for numerous reasons. It is possible that these associations are weaker during young adulthood as compared to during childhood development or aging. Previous studies (Chaddock-Heyman et al., 2015; Oberlin et al., 2015) also used superior measures of fitness (e.g., direct assessment of maximal oxygen uptake during a graded exercise test), which may have provided better measurement of fitness, and in turn, of the true association with brain structure. It is also possible that the large sample size of the current study allowed us to avoid detecting false positive findings. An underappreciated phenomena is that small studies, in which constructs are measured with error (as is ubiquitous in the behavioral and neurocognitive sciences), are prone to overestimate effect sizes, leading to false positives, in addition to being prone to failure in detecting effects (Loken and Gelman, 2017). This is especially true when the publication of research findings is contingent of the findings being statistically significant. To resolve the inconsistencies of the current study with previous ones, large-sample, lifespan studies with gold-standard measures of physical fitness are needed; the result will be better estimation of the associations between fitness and brain structure and determination of how these associations might change over the life course.

Behavioral Genetics of Body Composition and Brain Structure

To further explore the nature of the association between BMI and brain structure, our study made use of the large set of twins and full siblings contained in the YA-HCP. Using behavioral genetic analyses, we estimated the degree to which variation in BMI and brain structure, and the covariation between BMI and brain structure, could be explained by heritability—i.e., a set of common genes that directly or indirectly impact BMI and brain structure—versus environmental effects. The first insight from these analyses was that a simpler behavioral genetic model, in which variation and covariation was partitioned into genetic versus environmental effects, fit the data no worse, despite being simpler, than a model which further apportioned environmental effects into twin-specific effects, more generally sibling shared effects, and non-shared environmental effects. Others have also found that this simpler model fits (co)variation in BMI and neurocognition well (Vainik et al., 2018; Wood et al., 2019). This would imply that shared environmental effects—whether specific to twins or to full siblings more generally—have little consistent contribution to any connections between BMI and brain structure.

The second insight from these behavioral genetic analyses is that there was a clear heritability effect underpinning variation in BMI and the identified brain structures, as well as the covariation between BMI and these brain structures. Indeed, this heritability effect exceeded the environmental effect across all variance and correlation estimates (see **Figures 6**, **7C**) and comports with previous studies that have observed a clear genetic effect on variation in BMI and neurocognition analyzed independently (Friedman et al., 2008; Elks et al., 2012; Kochunov et al., 2015), as well as in studies that employed bivariate behavioral genetic analyses similar to the current study (Vainik et al., 2018; Wood et al., 2019).

This heritability effect is the portion of the variance or covariance that can be attributed to an additive genetic effect after adjusting for the covariates. Although heritability estimates provide some insight as to how various phenotypes (say, BMI and brain structure) are related, there is still a large degree of ambiguity about the nature of these associations. This clear heritability effect could reflect a common set of genes that causally affect both BMI and brain structure, so-called genetic confounding or pleiotropy (Vainik et al., 2018). If genetic confounding largely accounts for the association between BMI and brain structure, intervening upon either phenotype would be expected to have little impact on the other phenotype. Alternatively, genetic effects could directly affect one phenotype that in turn, through active selection of environments and behaviors, impacts the second phenotype (Scarr and Mccartney, 1983). If our heritability estimate truly reflects a cascading effect where genetic effects are transmitted through an intermediary phenotype, there is evidence in the literature that the cascade could flow in either direction. One possibility is that differences in brain structure impact obesogenic behaviors through decision-making processes, and in turn, leads to variation in BMI (Alonso-Alonso and Pascual-Leone, 2007; Lowe et al., 2019). Under this proposed directionality, it may be helpful to remediate decision-making processes in order to promote healthful behavior or structure the environment to support healthful behaviors and reduce the reliance of individual decision-making (Hall and Fong, 2015; Hall, 2016), all with the intent of reducing obesity. Alternatively, BMI might impact brain structure via cardiometabolic effects, including inflammation and hypertension (Williamson et al., 2018; Repple et al., 2019). Interventions to reduce BMI might have the added benefit of improving brain structure, especially WM integrity, though evidence from clinical trials is lacking (Wassenaar et al., 2019). It may also be worthwhile to intervene on the cardiometabolic consequences of excess weight. A recent clinical trial showed that intensive blood pressure treatment reduced the accrual of WM lesions over time among hypertensive adults 50 years or older (Nasrallah et al., 2019).

A final note from the behavioral genetic analyses is that although generally smaller in size, the environmental contributions to (co)variation in BMI and brain structure were not negligible. Thus, it is possible that environmental exposures (e.g., diet, physical activity) that operate outside of genetic selection of environments make a meaningful contribution to the association between body composition and brain structure.

Limitations

The current study has noteworthy limitations and the findings are conditioned on certain untested assumptions. The cross-sectional study design prohibits us from understanding the causality or even directionality of the association between BMI and brain structure. As noted above, even a strong heritability effect is consistent with various causal models of the studied variables. Our physical fitness and body composition measures also have limitations. Physical fitness was measured less precisely than gold-standard measures, such as maximal oxygen uptake during a graded exercise test. BMI was calculated using self-reported height and weight, and further BMI is an imperfect proxy for actual body composition (e.g., percentage of body fat or amount of central adiposity), which have stronger negative cardiometabolic sequelae (Frankenfield et al., 2001). Our behavioral genetic analyses require the untested assumptions that there is no assortative mating (i.e., individuals are not mating with others with similar BMI or brain structure more than expected at random) and that the environmental effects are equivalent across sibling pair type.

CONCLUSION

Our study adds to a fairly consistent pattern of findings showing that higher BMI correlates with lower WM integrity at various points in the lifespan [summarized in Wassenaar et al. (2019)]. We also extend the current literature in other ways. By taking a comprehensive approach to analyzing fitness and body composition with several structural markers of brain health, we show that BMI, but not strength or endurance, uniquely correlates with WM integrity, and that there was very limited evidence for an association with GM structure. A final contribution of the current work stems from findings from our behavioral genetic analyses of twins and full siblings. These analyses confirm previous studies by showing that heritability contributes to a majority proportion of variation in BMI and brain structure. Furthermore, we show that generally at least $\frac{1}{2}$ of the correlation between BMI and brain structure can be attributed to heritability. This does not imply that either BMI or brain structure is immutable, but it does improve our understanding of the etiology of the association between BMI and brain structure.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://db.humanconnectome.org.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board at Simon Fraser University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JB conceptualized the study, acquired the data, conducted the statistical analyses, and wrote the first draft of the manuscript. ED contributed to analysis and interpretation of neuroimaging results. RC acquired and synthesized literature necessary to the Introduction and Discussion sections. TC contributed to the conceptualization and interpretation of the study. All authors provided critical feedback and editing to the submitted 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/fpsyg.2020.608049/full#supplementary-material

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Impact of Weekly Physical Activity on Stress Response: An Experimental Study

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The aim of this research is focused on analyzing the alteration of the psychophysiological and cognitive response to an objective computerized stress test (Determination Test - DT-, Vienna test System®), when the behavioral response is controlled. The sample used was sports science students (N = 22), with a mean age of 22.82 (M_{age} = 22.82; SD_{years} = 3.67; $M_{PhysicalActivity\ hours/Week}$ = 7.77; $SD_{hours/week}$ = 3.32) A quasi-experimental design was used in which the response of each participant to the DT test was evaluated. The variable "number of hours of physical activity per week" and the variable "level of behavioral response to stress" were controlled. Before and after this test, the following parameters were measured: activation and central fatigue (Critical Flicker Fusion Threshold (CFF Critical flicker fusion ascending and Critical flicker fusion descending; DC potential), and perceived exertion (Central Rating of Perceived Exertion and Peripheral Rating of Perceived Exertion). Significant differences were found in all of the measures indicated. The usefulness of this protocol and the measures used to analyze the stress response capacity of the study subjects are discussed.

Keywords: central fatigue, omega wave, cognitive response, psychophysiology, stress

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INTRODUCTION

The analysis of psychophysiological fatigue is considered very important in different contexts (Lohani et al., 2019). In this sense, the consideration of the study of humans's response to external and internal loads (Wijesuriya et al., 2007; Wilson et al., 2007) has become one of the most important research topics. The external loads exerted on the individual are added to their skills and coping strategies, resulting in a level of tolerance and adaptation to each situation (Folkman and Lazarus, 1988). Along the last decades, distinctions are often made between physical and mental fatigue role, indicating clear methodologies for the analysis of physiological fatigue, but with clear limitations in the study of central fatigue, because this is measurable only indirectly, which emphasizes the importance of developing new central fatigue analysis procedures (Bittner et al., 2000).

Throughout the decades of research on this topic, different strategies have been used to evaluate the adaptation to these external and internal loads (Lazarus, 1990; Amann, 2011). Thus, for example, a multitude of self-reports and standardized tests have been used (Britner et al., 2003), to which physiological and biological measures have been added (Arza et al., 2019). However, relatively low attention is usually given to the Central Nervous System (CNS)-related mechanisms, which play a major role on the development of fatigue (Tarvainen et al., 2014), but are rarely monitored in the sport and physical activity field (Valenzuela et al., 2020). Most of the studies related to central fatigue to date have focused on the effect it has on performing strenuous physical tasks (Amann and Dempsey, 2008), although over the last few years there has been a notable increase in interest in studying the role of central fatigue in explaining human performance (Inzlicht and Marcora, 2016). In this sense, the psychobiological model based on motivational intensity theory has gained special strength (Gendolla and Richter, 2010). This model emphasizes that perception of effort and potential motivation are the central determinants of task engagement. Both variables are taken into consideration in our research, controlling the involvement in the task (motivation), by applying a computerized test, and analyzing the perception of both central and peripheral effort as detailed in the methodological section.

Two of these measures, which focus the methodological attention of this research due to its great potential in the study of this topic, are the Critical Flicker Fusion Threshold (CFFT), evaluated using one Flicker Fusion instrument (Vicente-Rodríguez et al., 2020), and the DC Potential, evaluated using the OmegaWave technology. The neuro-physiological basis of flicker perception is complex but well established (Görtelmeyer and Zimmermann, 1982). In particular, flickering light directly influences cortical activity. The CFFT was measured using two red light- emitting diodes in binocular foveal fixation. The continuous psychophysical method of limits was employed to determine CFFT (Woodworth and Schlosberg, 1954). The utility of CFFT in sport has been focused on the relationship of arousal level with CNS (Görtelmeyer and Zimmermann, 1982). Increase in CFFT suggests an increase in cortical arousal and sensory sensitivity. By contrast, a decrease of CFFT suggests a reduction in the efficiency of the system to process information (Li et al., 2004; Clemente and Díaz, 2019). On the other hand, for the evaluation of the brain's direct current (DC) potentials -slow potentials that reflect alterations in brain excitability-OmegaWave technology has gained strength in recent years (Naranjo-Orellana et al., 2020; Valenzuela et al., 2020). This device not only measures the Heart Rate Variability (HRV) but it also simultaneously a brainwave signal (DC potential) in order to complement the information obtained from HRV to assess the athlete's functional state (Naranjo-Orellana et al., 2020). DC potentials—frequency ranges between 0 and 0.5 Hz, are correlated with different brain processes, such as take consciousness during decision making (Guggisberg and Mottaz, 2013) high alertness states (Bachmann, 1984), arousal state (Haider et al., 1981), or attention (Rösler et al., 1997).

To date, most studies conducted in the evaluation of central fatigue have shown that the greatest disturbances are produced by tasks that require efforts at maximum speed that involve a large amount of force (Davranche and Pichon, 2005; Clemente and Díaz, 2019). However, there are very few studies that have analyzed central fatigue through controlled analysis of a task that primarily involves central fatigue (Fuentes et al., 2019). In this sense, the aim is to apply a computerized test (DT, Vienna Test System), that allows evaluating people's tolerance to stress and central fatigue by applying a standardized protocol, in physical activity practitioners. The knowledge in this field is really limited, for this reason we developed the present research with the aim of studying the modifications in CFFT and DC potentials in a sample group of regular physical activity. The first hypothesis establishes that the computerized stress task increases the participants' perception of central fatigue, while keeping the perception of peripheral fatigue stable. As a consequence, the second hypothesis establishes that differences will be found in the "post" situation in the CFFT measures and in the central physiological indicators, which would indicate a relationship between the subjective and objective measures of central fatigue.

MATERIALS AND METHODS

This study followed a quasi-experimental design (Montero and León, 2007) and it received the approval of the University Ethical Commission in compliance with the Helsinki Declaration. All subjects were informed about the procedure and gave their written consent to participate. This study was carried out complying with the Standards for Ethics in Sport and Exercise Science Research (Harriss et al., 2019).

Participants

The participants included 22 individuals from Madrid (Spain), 18 of whom were male and 4 females. These participants were aged between 18 and 36 years (M_{years} = 22.82, SD_{years} = 3.67). All of the participants regularly engaged in physical activity, between 4 and 14 h per week ($M_{\text{hours/week}}$ = 7.77, $SD_{\text{hours/week}}$ = 3.32). The inclusion criteria was that they performed physical activity at least 3 times a week and 150 min of moderate/vigorous physical activity. The exclusion criteria was not correctly performing the proposed measurements. Four participants were excluded from the study for not completing the measurements correctly. Intentional sampling methods were used (Montero and León, 2007). Due to the impossibility of continuing with the data collection due to the Alert State decreed by the Spanish Government as a result of COVID-19, the sample had to be closed with the participants who had passed all the tests before March 2020.

Instrumentation and Study Variables

The number of hours of physical activity per week and the scores obtained on the DT test were used as controlled variables. This allows us to know that the differences found are not due to the ability to respond to stress, or to the weekly amount of physical exercise performed. Therefore, only the subjects in which there were no statistically significant differences in their weekly level of physical exercise, nor in the scores obtained in the DT test, were used.

To carry out this research, three measurement systems have been used: OmegaWave device, Flicker Fusion Unit (Vienna Test System), and the Determination Test (Vienna Test System).

OmegaWave is a device that assesses the physiological readiness of athletes by examining the autonomic balance through HRV and brain‘s energy balance via DC potential (Gómez-Oliva et al., 2019), Elastic chest band MEDITRACE (dominant hand and forehead). Coach + application (OmegaWave Ltd, Espoo, Finland) was used on Ipad mini 2 32GB. The Vienna Test System is an instrument for computerized psychological assessments that allows the objective evaluation of different psychological parameters. The Determination Test (DT Vienna test system) (Whiteside, 2002; Whiteside et al., 2003) was used to determine neuropsychological fatigue. The test studied the attentional capacity, reactive stress tolerance, reaction speed among continuously, and quickly changing acoustic and visual stimuli. The test is simple, the difficulty of the task lies in the different modality of the arriving stimuli and their speed. This way we measure those cognitive abilities of the people involved that are needed for the distinction of colors and sounds, the perception of the characteristics of stimuli, their memorization, and finally, the selection of the adequate answer. The stimuli coming during the test are not predictable. Instead, the subjects need to react to them randomly (Schuhfried, 2013). We study four key variables: the average value of reaction speed (sec), the number of correct answers (raw score), which reflects the ability of the respondent to precisely and quickly select the adequate answer even under pressure. Furthermore, we also examine the number of incorrect answers (raw score) which can show us how likely the respondent is to get confused under stress and pressure; finally, the high number of missed answers (raw score) reveals that the respondent is not capable of maintaining his/her attention under stress and is prone to giving up these situations (Neuwirth and Benesch, 2012). The duration of this test was 6 min.

Before and after the stress test the following parameters were analyzed in this order:

Parameters analyzed through OmegaWave Coach + device® (OmegaWave Ltd, Espoo, Finland):

- Hear Rate Variability (HRV). Square root of the mean of the squares of successive RR interval differences (RMSSD), Standard deviation of all normal to normal RR intervals (SDNN), and Standard deviation of successive squares of intervals RR (SDSD). OmegaWave is a device that assesses the physiological readiness of athletes by examining autonomic balance through HRV and brain‘s metabolic state via DC potential (Ilyukhina and Zabolotskikh, 2020). Elastic chest band MEDITRACE (dominant hand and forehead). Coach + application (Omegawave Ltd., Espoo, Finland) was used on Ipad mini 2 32GB. For calculating HRV it be used the Root Mean Square of the Successive Differences score (RMSSD) (Ilyukhina et al., 1982). It was used before and after the stress test.
- DC potential dynamics. DC Potential represent changes in the brain's metabolic balance in response to increased exercise intensity or psychological challenges and are linked to cognitive and mental load (Wagshul et al., 2011; Ilyukhina, 2015).
- CNS System Readiness (Ilyukhina, 1986). It's indicated by a floating grade from 1.0 to 7.0, where 7.0 is the optimal state. This index represents the state of the brain's energy level and is composed of three factors (in order of significance): stabilization point of DC potential (mV), stabilization time (reduces system readiness state of 1.0–7.0, if not optimal), and curve shape (reduces system readiness state of 1.0–7.0, if not optimal).
- Stabilization point of DC Potential (mV) (Ilyukhina et al., 1982; Ilyukhina, 2013): The first priority in DC analysis is the stabilization point of DC Potential. In the literature, especially by Ilyukhina, this point is defined as Level of Operational Rest. In 1982, the combined work of Ilyukhina and Sychev was published which outlined quantitative parameters of LOR for the assessment of the healthy human's adaptation and compensatory—adaptive abilities to physical and mental loads in sports.
- Stabilization time (Ilyukhina and Zabolotskikh, 1997). The second priority of analysis is to look at the stabilization time. measured in minutes. The spontaneous relaxation speed represents neuroreflex reactivity (neural control of baroreflex arch) of cardiovascular and respiratory systems. This measure associated with psycho-emotional dynamic and stability. Normal stabilization time occurs within 2 min and represents optimal balance within stress-regulation systems.
- Curve Shape: The curve shape is composed of two elements: Difference between measurement start mV and end mV values (**Table 1**). The optimal shape of the curve should show a smooth transition from a higher initial value (active wakefulness) to a lower stabilization value (operational rest DC potential form represents the dynamic interaction within stress-regulation systems). DC potential form can indicate the level of CNS activation balance.

Parameters analyzed though Flicker Fusion unit (Vienna Test System®):

- Critical flicker fusion ascending (Hz) (CFFA) and Critical flicker fusion descending (Hz) (CFFD). Cortical arousal was measured using the critical flicker fusion threshold (Hz) (CFFT) in a viewing chamber (Vienna Test System®), following the procedure of previous studies (Clemente et al., 2016). An increase in CFFT suggests an increase in cortical arousal and information processing; a decrease in CFFT values below the baseline reflects a reduction in the efficiency of information processing and central nervous system fatigue (Whiteside, 2002). It was used before and after the stress test.

TABLE 1 | Simplified curve change mV reduction algorithm.

Start mV—End mV Diff	Grade of reduction to OverallDC
18.0–45.0 mV	No impact
45.0 mV–55 mV or 7.5–18 mV	Moderate reduction
Below 7.5 mV or more than 55 mV	Significant reduction

Parameters analyzed though DT test (Vienna Test System®):

- We study four key variables: the average value of reaction speed (msec), the number of correct answers (raw score), which reflects the ability of the respondent to precisely and quickly select the adequate answer even under pressure. Furthermore, we also examine the number of incorrect answers (raw score) which can show us how likely the athlete is to get confused under stress and pressure; finally, the high number of missed answers (raw score) reveals that the respondent is not capable of maintaining his/her attention under stress and is prone to giving up these situations (Neuwirth and Benesch, 2012). The duration of this test was 6 min without instructions.

Parameters analyzed by self-report instruments:

- Central Rating of Perceived Exertion (RPEC) and Peripheral Rating of Perceived Exertion (RPEP). The Rating of Perceived Exertion (Borg, 1998), was used as a measure of central (cardiorespiratory) and peripheral (local-muscular, metabolic) exertion before and after the stress test (Bolgar et al., 2010; Cárdenas et al., 2017). The RPE is a 15 point category-ratio; the odd numbered categories have verbal anchors. Beginning at 6, "no exertion at all," and goes up to 20, "maximal exertion." Before testing, subjects were instructed on the use of the RPE scale (Noble and Robertson, 1996). We use the scale with the clear differentiation between central as peripheral perceived exertion following the recommendations of the medical staff and under the guideline of Borg (Borg, 1982), for applied studies.

Procedure

The participants were contacted and informed about the measurement protocol and of the date and time of the data collection. All of the measurements were collected during the same day. The total data collection time per participant was approximately 45 min. The order of measurements was the following: CFFT, DC Potential, RPE, DT test, RPE, CFFT, and DC Potential.

Statistics

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 21 (SPSS Inc., Chicago, Ill., United States). Means and SDs were calculated using traditional statistical techniques. Normality was tested with the Shapiro-Wilk test. As the distributions were not adjusted to the normal, non-parametric tests were used. A Wilcoxon sign ranges test for intragroup comparisons were conducted to analyze differences between pre and post-test. A Rho Spearman coefficient was used to know the correlations between variables. The Effect Size was tested using the formula = $Z/\sqrt{N}$ for non-parametric tests (Tomczak and Tomcak, 2014). Following the considerations of Cohen (1988), the effect size is considered small when the value is inferior to 0.10, medium when it varies between 0.10 and 0.30 and high when it is superior to 0.50. The significance level was set at $p < 0.05$.

RESULTS

Descriptive Analysis, Normality Test According N, Wilcoxon Test, and Effect Sizes

Firstly, the normality tests were realized with the Shapiro-Wilk test. It was determined that most of the variables were not normal, due to which non-parametric statistical tests were applied. In relation to the descriptive analyzes of the study variables, shown in **Table 2**, after applying the stressor via the DT test, worse values were obtained in all the variables measured. This reflects the alterations in the central response evaluated. Regarding the Wilcoxon rank test that was used to analyze whether there were differences between the scores obtained before and after applying the stressor (DT test), significant differences were found in the variables OverallDc ($p < 0.05$), Flicker ascending ($p < 0.01$), Flicker descending ($p < 0.01$), Central RPE ($p < 0.01$) and Physical RPE ($p < 0.01$), while not finding significant differences in the rest of the variables (**Table 2**).

TABLE 2 | Descriptive analysis of the measured variables.

Variables	M[a]	SD[b]	S-W[c]	Z[d]	Sig	Effect size
OverallDC (pre-test)	3.62	1.32	0.17	−2.21	0.02	0.47
OverallDC (post-test)	3.07	1.37	0.36			
CNS System (pre-test)	4.68	1.29	0.04	−1.20	0.23	0.25
CNS System (post-test)	4.36	1.17	0.00			
Stabilization DC (pre-test)	7.84	8.59	0.03	−1.83	0.06	0.39
Stabilization DC (post-test)	5.42	10.60	0.01			
Stabilization Time (pre-test)	154.52	49.23	0.00	−0.34	0.74	0.07
Stabilization Time (post-test)	157.75	52.86	0.00			
Curve Shape (pre-test)	6.06	1.25	0.00	−0.41	0.68	0.08
Curve Shape (post-test)	5.93	1.29	0.00			
CFFA (pre-test)	36.63	2.88	0.00	−3.72	0.00	0.79
CFFA (post-test)	38.05	2.89	0.01			
CFFD (pre-test)	38.805	2.64	0.04	−2.37	0.01	0.50
CFFD (post-test)	37.99	3.38	0.03			
RPEC (pre-test)	9.55	2.13	0.25	−4.11	0.00	0.88
RPEC (post-test)	14.55	2.22	0.36			
RPEP (pre-test)	9.18	2.32	0.13	−3.56	0.00	0.76
RPEP (post-test)	10.82	2.40	0.04			
RMSSD (pre-test)	62.29	28.35	0.94	−0.34	0.73	0.07
RMSSD (post-test)	61.02	24.12	0.83			
SDNN (pre-test)	71.15	26.11	0.04	−1.05	0.29	0.22
SDNN (post-test)	68.04	24.77	0.01			
SDSD (pre-test)	78.42	35.62	0.10	−0.44	0.66	0.09
SDSD (post-test)	76.93	30.68	0.82			
DT_MTR	0.70	0.05	0.48			
DT_CR	551.23	44.79	0.11			
DT_IR	38.50	30.57	0.00			
DT_O	24.36	13.28	0.23			

[a] *Media.*
[b] *Standard Deviation.*
[c] *Shapiro–Wilks.*
[d] *Wilcoxon sign ranges test.*

Correlation Analysis

A Spearman bivariate correlation analysis was performed. Spearman's Rho coefficient was used, since the distribution was non-parametric. Note that significant correlations were found (**Table 3**) entre OverallDC con DCSSatabilizationLevel (p = 0.000; r = 0.791**); OWCNS (p = 0.005; r = 0.581**); OWDCC (p = 0.013; r = 0.522*); Flicker Descending (p = 0.044; r = 0.432*). DCSStabilizationLevel con OWCNS (p = 0.000; r = 0.766**); Flicker Descending (p = 0.049; r = 0.424*). DCSStabilizationTime con OWCNS (p = 0.005; r = 0.572*); OWDCC (p = 0.046; r = 0.430*); Flicker Ascending (p = 0.006; r = 0.563**). OWCNS correlated with Flicker Ascending (p = 0.018; r = 0.499*), and SDSD with Flicker Descending score (p = 0.046; r = −0.430*).

DISCUSSION

The objective of the present research was to study the modification of DC potentials and the CFFT scores after the computerized stress test (DT). The analysis of the subjective cognitive responses about fatigue after DT test reveals significant differences in the participants, both at a physical and central level. As regards the first hypothesis, it is partially fulfilled. There are significant differences in central perceived fatigue, with a very high effect size, which supports the hypothesis and emphasizes the usefulness of the established research protocol. However, significant differences also appear in peripheral perceived fatigue, which is beyond the initial approaches. This result is of special interest because it allows to consider the relationship between both types of perceived fatigue (Bittner et al., 2000; Clemente et al., 2016). These results, taking into account that the participants did the test sitting down, emphasize the effect achieved through the protocol used to generate stress in them, without significant differences in the performance achieved in the task. Previous research carried out with the DT test already points in this same direction (Ong, 2015). The differences found in the perception of physical fatigue even without previous movement are interesting. Similar results are found in studies carried out in contexts such as chess (Fuentes et al., 2019), where central fatigue due to the demands of each game also leads to physical fatigue of the players. This fact seems relevant insofar as the studies should incorporate measures of both dimensions to be able to explain a higher percentage of variance of the results found.

As regards the second hypothesis, the decrease of CFFD values indicates that it has a negative effect generating central fatigue and an alteration in cortical activation (Li et al., 2004; Clemente, 2016). These results confirm the alterations in cortical activation found in physiological efforts of high intensity and of short duration, such as sprints at maximum speed (Clemente et al., 2011). This same trend is also observed in research focused on generating a high level of stress in soldiers, which emphasizes the usefulness of using the DT test to create stress in the participants (Clemente et al., 2016). In line with the ideas defended by Clemente (2016), decreased in CFFD scores seem to be linked to high sympathetic autonomous nervous system activation, which could also affect higher cognitive functions, such as executive processes (i.e., making complex decisions, memory, and attention processes) (Shields et al., 2016). These same considerations can also be made with respect to the significant differences found in CFFA scores. Higher scores are found after the stress test, which implies that the participants have needed more time to respond to the flicker task as consequence of central fatigue (Fuentes et al., 2019; Lohani et al., 2019).

Regarding the results obtained in the Overall DC scores, the significant differences show a pattern of alteration as a consequence of the stress test. As Naranjo-Orellana et al. (2020) point out, the OW test obtains good reliability and validity values using the heart rate variability as a measure in conjunction with the DC Potential (stabilitation DC, stabilitation time, and curve shape). Changes in the DC potentials have been reported to be reflective of performance in different brain processes (Haider et al., 1981; Valenzuela et al., 2020). The lower scores obtained after the stress test could indicate, as with the CFF scores, an increase in central fatigue detected by the OmegaWave system

TABLE 3 | Rho Spearman coefficient.

Variables	1	2	3	4	5	6	7	8	9	10	11	12
OverallDC	1.00	0.791**[a]	0.58**	0.40	0.52*[b]	0.36	0.43*	−0.16	0.08	0.10	0.04	0.85
CNS System	0.58**	0.76**	1.00	0.57**	0.15	0.49**	0.27	−0.26	−0.07	0.11	0.01	0.10
Stabilization DC	0.791**	1.00	0.76**	0.32	0.11	0.22	0.42*	−0.29	−0.02	0.08	0.05	0.07
Stabilization Time	0.40	0.32	0.57**	1.00	0.43*	0.56**	0.38	0.07	0.13	−0.09	−0.14	−0.13
Curve Shape	0.52*	0.11	0.15	0.43*	1.00	0.27	0.06	0.13	0.19	0.12	−0.05	0.09
CFFA	0.36	0.22	0.49**	0.56**	0.27	1.00	0.39	−0.18	0.17	−0.12	−0.18	−0.13
CFFD	0.43*	0.42*	0.27	0.38	0.06	0.39	1.00	−0.16	−0.03	−0.41	−0.41	−0.43*
RPEC	−0.16	−0.29	−0.26	0.07	0.13	−0.18	−0.16	1.00	0.41	0.01	0.18	0.00
RPEP	0.08	−0.02	−0.07	0.13	0.19	0.17	−0.03	0.41	1.00	−0.42	−0.29	−0.41
RMSSD	0.10	0.08	0.11	−0.09	0.12	−0.12	−0.41	0.01	−0.42	1.00	0.89**	0.99**
SDNN	0.04	0.05	0.01	−0.14	−0.05	−0.18	−0.41	0.18	−0.29	0.89**	1.00	0.87**
SDSD	0.85	0.07	0.10	−0.13	0.09	−0.13	−0.43*	0.00	−0.41	0.99**	0.87**	1.00

[a] *$p < 0.01$.
[b] **$p < 0.05$.

(Valenzuela et al., 2020). This result, in any case, needs to be analyzed in detail in future research.

Therefore, monitoring the DC potentials and the CFF scores could be useful to control the cognitive load of the different tasks that having a high mental demand.

Due to the exceptional circumstances of data collection in the present study, some of the study limitations were the sample size and the small number of women who participated in it. Future research works should expand the sample power, as well as determine its effect in a sedentary sample.

CONCLUSION

To conclude, this is the first study that has jointly analyzed the scores obtained in the analysis of low-frequency brain waves (DC potentials), together with those obtained in the Flicker test. In this sense, although the performance in a specific task seems similar, the demand it has for the person must be evaluated, being useful the use of research protocols similar to the ones we have used. The results open a new field where both measurements could be interesting and useful to assess the cognitive demands of persons.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University Ethical Commission in compliance with the Helsinki Declaration. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RV: conceptualization, investigation, resources, writing—review and editing, and project administration. RV, ML-R, and RJ-C: methodology, data curation, writing—original draft preparation, visualization, supervision, and formal analysis. ML-R and RJ-C: software and validation.

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ORIGINAL RESEARCH
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Behavioral and ERP Correlates of Long-Term Physical and Mental Training on a Demanding Switch Task

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Physical and mental training are associated with positive effects on executive functions throughout the lifespan. However, evidence of the benefits of combined physical and mental regimes over a sedentary lifestyle remain sparse. The goal of this study was to investigate potential mechanisms, from a source-resolved event-related-potential perspective, that could explain how practicing long-term physical and mental exercise can benefit neural processing during the execution of an attention switching task. Fifty-three healthy community volunteers who self-reported long-term practice of Tai Chi (n = 10), meditation + exercise (n = 16), simple aerobics (n = 15), or a sedentary lifestyle (n = 12), aged 47.8 ± 14.6 (SD) were included in this analysis. All participants undertook high-density electroencephalography recording during a switch paradigm. Our results indicate that people who practice physical and mental exercise perform better in a task-switching paradigm. Our analysis revealed an additive effect of the combined practice of physical and mental exercise over physical exercise only. In addition, we confirmed the participation of frontal, parietal and cingulate areas as generators of event-related-potential components (N2-like and P3-like) commonly associated to the performance of switch tasks. Particularly, the N2-like component of the parietal and frontal domains showed significantly greater amplitudes in the exercise and mental training groups compared with aerobics and sedentary groups. Furthermore, we showed better performance associated with greater N2-like amplitudes. Our multivariate analysis revealed that activity type was the most relevant factor to explain the difference between groups, with an important influence of age, and body mass index, and with small effects of educational years, cardiovascular capacity, and sex. These results suggest that chronic combined physical and mental training may confer significant benefits to executive function in normally aging adults, probably through more efficient early attentional processing. Future experimental studies are needed to confirm our results and understand the mechanisms on parieto-frontal networks that contribute to the cognitive improvement associated with practicing combined mental and aerobic exercise, while carefully controlling confounding factors, such as age and body mass index.

Keywords: executive function, switching, EEG sources, ERP, physical-mental practice

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INTRODUCTION

Research studies on the benefits of physical and mental training have shown a positive effect on cognitive function throughout the lifespan (Kramer et al., 1999; Chan and Woollacott, 2007; Weinstein et al., 2012; Hawkes et al., 2014a). Many types of exercise have been studied: golf (Shimada et al., 2018), dance, (Chuang et al., 2015; Eggenberger et al., 2015), aerobic and resistance training (Kramer et al., 1999; Lucas et al., 2012; Weinstein et al., 2012; Chapman et al., 2013; Steinberg et al., 2015; Tsai et al., 2018; Wu et al., 2019), Tai Chi (Matthews and Williams, 2008; Hawkes et al., 2014a) and the mental training required for meditation (Chan and Woollacott, 2007; Moore and Malinowski, 2009; Zeidan et al., 2010; Moynihan et al., 2013; Elliott et al., 2014; Raichlen and Alexander, 2017).

Though research studies on the individual effects of physical and mental training report improvement in cognitive function, research on combined physical and mental training—such as Tai Chi, dancing, sports, and other exercise disciplines that combine the simultaneous practice of cognition + moderate exercise—suggests increased benefits compared to exercise that does not require attention, planning, memory or other cognitive challenge (Matthews and Williams, 2008; Voss et al., 2009; Anderson-Hanley et al., 2012; Maillot et al., 2012; Hawkes et al., 2014a; Wayne et al., 2014; Zhu et al., 2016; Raichlen and Alexander, 2017). Evidence for cognitive improvement resulting from combined mental and physical training in humans is mainly behavioral considering different kinds of cognitive challenges and the simultaneous or delayed performance of physical and cognitive practice (Anderson-Hanley et al., 2012; Barcelos et al., 2015; Eggenberger et al., 2015). Also, there is evidence that the combined regimes have advantages over the physical but not over a pure cognitive training (Raichlen and Alexander, 2017). Thus, more research is needed to elucidate how physical and mental exercise affects the neural processes underlying cognitive function (Bamidis et al., 2014; Raichlen and Alexander, 2017).

The current study is a secondary data analysis of data collected from a cross-sectional observational study that evaluated differences in cardiovascular and executive attention metrics across groups self-reporting adherence to different health regimes (Hawkes et al., 2014a,b)—Tai Chi, meditation + exercise, and simple aerobics (e.g., walking, jogging). A sedentary control group was included. Hawkes et al. (2014a) reported that Tai Chi and meditation + exercise practitioners had statistically faster reaction times, lower local switch costs, and greater P300 event-related-potential (ERP) amplitudes compared to sedentary controls, but not the aerobic practitioners, who performed similar to the sedentary controls. These results are in line with the previous literature; there is evidence for larger P3b amplitudes in elderly adults who practiced moderate aerobic exercise compared to sedentary elderly controls (Hillman et al., 2004). Hillman et al. (2006, 2003) also reported larger P3b amplitudes and shorter latencies on a task-switching paradigm in active versus inactive young and older adults. Meditation studies have also shown increased ERP amplitude or decreased latency during tasks requiring attentional focus and distractor inhibition (Slagter et al., 2007). Van Leeuwenn et al. reported larger N1, N2, P1, and P3 ERP amplitudes in meditators compared to controls during an attentional task (van Leeuwen et al., 2012). Larger ERP amplitudes may index more attentional resources allocated during the updating of working memory, and shorter latencies may index more efficient neural processing (Hillman et al., 2006, 2003).

Several advances in the study of source brain activity (Onton et al., 2006; Makeig and Onton, 2011; Akalin Acar et al., 2013; Bigdely-Shamlo et al., 2013) allow separate weighted-combinations of mean event-related activities arising from several to many cortical sources that are mixed on scalp ERPs channels. Therefore, the aim of the present study was to investigate potential mechanisms, from a source-resolved ERP perspective, that could explain how practicing long-term physical and mental exercise can benefit neural processing during the execution of an attention switching task. In addition, we performed an analysis of the lifestyle and demographic factors of the groups in relation to the switching performance and the associated ERP activity that could also contribute to the group differences observed.

We hypothesized that this new source analysis would reveal health regime differences on source-ERPs with probable source in the prefrontal, parietal and anterior cingulate cortex, as previous functional magnetic resonance imaging (fMRI) studies have shown the relevance of these areas for improved attentional and executive function in both meditators and Tai Chi practitioners (Posner et al., 2007; Xue et al., 2011; Craigmyle, 2013; Guleria et al., 2013; Wei et al., 2014). Our results confirmed our hypothesis and suggest that a potential mechanism through which combined physical and mental exercise may favor cognitive performance is by facilitating early attentional processing in parieto-frontal networks.

MATERIALS AND METHODS

Participants

Fifty-three participants from the primary study (Hawkes et al., 2014a) living independently without neurological or physical disorders were included. The original study recruited participants with a wide age range (22–75) as one of the original aims was to study the effect of aging on cognitive performance. However, most of the participants belonged to the middle age range (44–65 years). The mean of age by groups is displayed in **Figure 1**, showing no differences between groups. The final sample for each group in this secondary data analysis was, Tai Chi (TC), $n = 10$; meditation + exercise (MEDe), $n = 16$; aerobic exercise (AER), $n = 15$; sedentary (SED), $n = 12$.

Subjects were recruited by flyers posted within Eugene, Oregon, online craigslist ads, and public service lectures on exercise as medicine in Eugene, Oregon area during the 2010–2011 years. All subjects were normally aging volunteers from Lane County, Oregon in which the city of Eugene is located. Health regimen practitioners (TC, MEDe, and AER) were required to have practiced at least 5 years or more, three times/week, 30 min/session. The commitment to the discipline was documented for all participants by means of a self-report

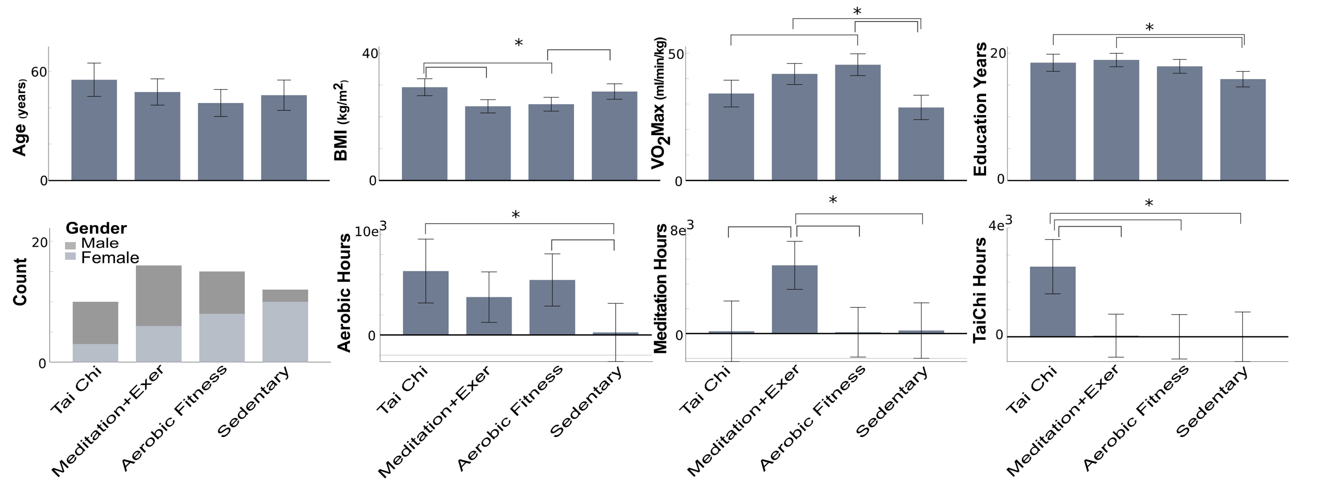

FIGURE 1 | Participant features by group disciplines. Mean and confidence interval at 0.95 by feature. VO_2 Max, estimated maximal oxygen uptake; BMI, body-mass index; Asterisk with brackets index: significant group differences ($p < 0.05$), the error bars represent the confidence interval.

questionnaire with number of days per week and minutes per session, as well as years they had practiced Tai Chi, meditation or aerobic activities. Sedentary participants were required to have been sedentary for five or more years, with no prior experience with meditation or Tai Chi. **Figure 1** indicates the number of hours practiced by participants, at the moment of the study, to either aerobic exercise, meditation or Tai Chi. The aerobic activities practiced by participants included, jogging, biking, and hiking. The meditation activities included both concentrative (e.g., focus on the breath) and open-awareness (e.g., practicing bringing awareness to the present moment) practices. Tai Chi training included a variety of styles, including Yang and Chen style Tai Chi. Physical + mental groups were considered (1) Tai Chi, because it integrates a variety of movement types, breath, and cognitive skills, including focused attention, imagery and multi-tasking; and (2) meditation + exercise, because meditators performed both the executive attention practice of focusing on the breath or keeping attention on the present moment and one of the aerobic exercises described above.

The University of Oregon Institutional Review Board approved the primary study. Written informed consent was obtained from all subjects. For more details see Hawkes et al. (2014a,b). Data analyzed in this study was de-identified.

Executive Attentional Task

Subjects performed a randomized alternating runs, non-cued visuospatial task switch test (VSTS) developed at the Mayr Laboratory, University of Oregon (Mayr, 2001). A computer display located 24 inches in front of the participant showed a red dot in a horizontally oriented fixation rectangle. Each subject was trained to respond as quickly and accurately as possible to stimulus appearance using a two-button mouse (**Figure 2A**). Rules 1 and 2 trained subjects to respond accurately to Rule 3, the task switching condition. Rule 1 required pressing the mouse button on the same side as the dot location on the screen. Rule 2 required pressing the button opposite to the dot's screen location. Rule 3, the condition evaluated in Hawkes et al. (2014a,b) and this study, required subjects to switch back and forth between rules 1 and 2 on each 2 trials (e.g., 1, 1, 2, 2, 1, 1, etc.). Thus, rule three comprised switch and no-switch trials which were used to calculate a behavioral index of the switching capacity of the participants as described below. Thus, the same trials were used as in the original ERP analysis, providing an index of the performance on the switch and no-switch conditions in Rule 3 and local switch costs, a normalized measure of the switching capacity from a behavioral response perspective. Visual error feedback was given to the participants, who continued with the task after they corrected their error. Twelve blocks of 48 trials each comprised the task switch condition (Rule 3). The test was programmed in E-Prime (Psychology Software Tools).

Participants' Physiological and Behavioral Performance Measures

Body mass index (BMI, body mass divided by height squared) and cardiovascular capacity (VO2max, estimated using the Rockport 1 mile walk) (Kline et al., 1987) are reported in **Figure 1**. Executive performance was evaluated with the VSTS task using percent local switch costs—calculated by subtracting non-switch (rule 3) from switch (rule 3) reaction time (RT), divided by non-switch (rule 3) RT (**Figure 2**). Local switch cost is a normalized measure that quantifies the difference between switch and non-switch trials for each group, while controlling for the speed/accuracy trade-off. Thus, this measure is a proxy for the ease with which switching between tasks occurs at the neural and behavioral levels. For more details see Hawkes et al. (2014a,b).

Electroencephalographic Acquisition, Preprocessing of EEG Data and ERPs

In the primary study, continuous electroencephalography (EEG) data were recorded in a Faraday cage protected room with a

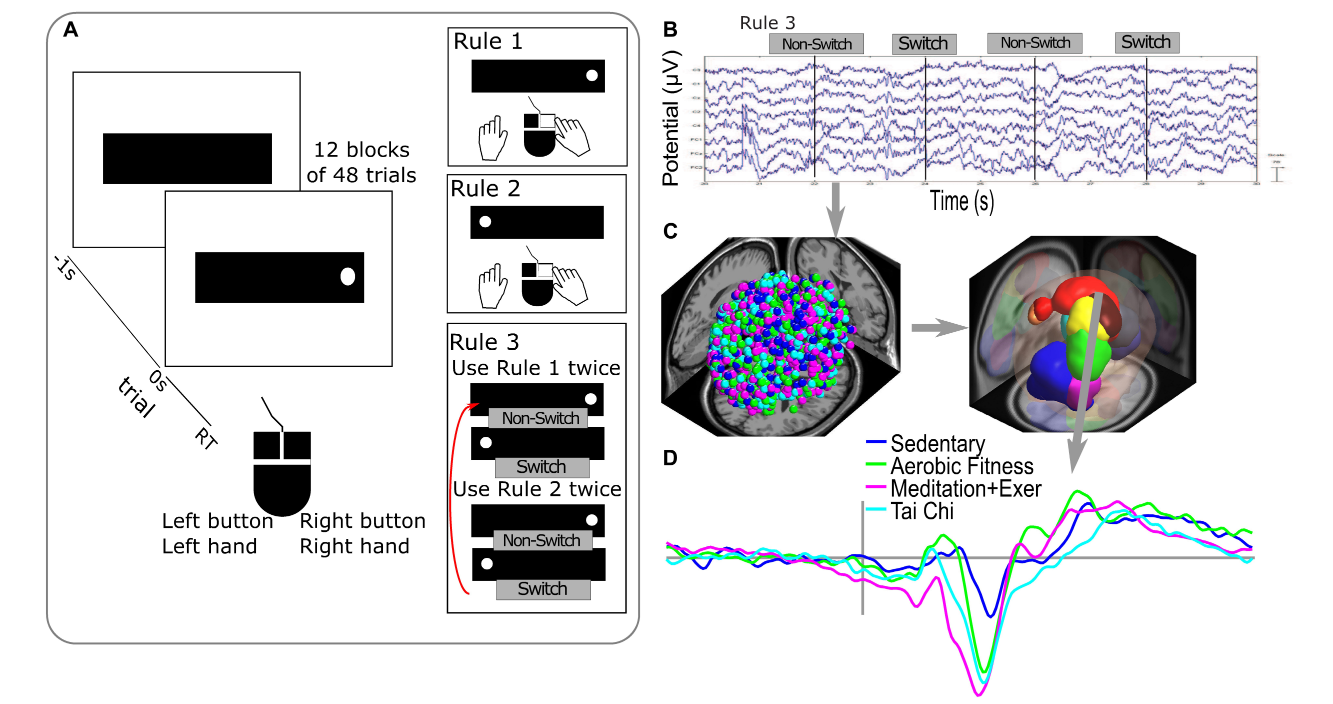

FIGURE 2 | Executive attentional task and EEG analysis. **(A)** Visuospatial switching task paradigm used in the study that consists of different rules during the responses with a two-button mouse. Rule 1 required pressing the mouse button on the same side as the dot location on the screen (time 0 s). Rule 2 required pressing the button opposite to the dot's screen location. Rule 3 required subjects to switch between rule 1 and 2 on each 2 trials. **(B)** Epochs of raw EEG signals used in the analysis were the correct responses for switch and non-switch trials from Rule 3 blocks. **(C)** Processing of EEG signals in sources dipoles (on the left side, dot colors represent all the dipoles obtained colored by groups) and clustering brain EEG sources dipoles in Brain Domains by similarities in location and ERP activity (measure projection domains are represented by colors blobs detailed in **Table 1**). **(D)** Example of ERP activity associated with one brain domain (superior frontal) representing the average by group in the color lines.

256-electrode Electrical Geodesics (EGI) EEG System 300 and digitized with a 24-bit A/D converter, collected at 250 Hz (EGI, Eugene, OR, United States). The impedance of each sensor was <5 KΩ. Channels were referenced to reference signal (VREF vertex) channel. Subjects were provided with a Table Clamp chin rest.

For this secondary analysis, EEG data were processed using the EEGLAB toolbox (Delorme and Makeig, 2004) in Matlab (The MathWorks, Inc.). Continuous data were filtered between 1 to 100 Hz; additionally, a notch filter was applied at 60 Hz to remove line noise. Independent Component Analysis (ICA) was performed on 128 of the 256 original channels to improve the quality of the ICA decomposition (Onton et al., 2006). We used the GSN-HydroCel-128 sensor position to select the 128 electrodes included in the ICA.

Data sets were automatically cleaned using the EEGLAB function clean_rawdata[1], with the following parameters, arg_flatline = off; arg_highpass = [0.25 0.75]; arg_channel = 0.8; arg_noisy = 4; arg_burst = 5; and arg_window = 0.3. Please see the limitations section of the discussion for possible limitations to the arg_burst preprocessing parameter. These multiple algorithms removed low-frequency-drifts, noisy channels, short-time burts and incompletely repaired segments from the data.

The ICA algorithm used was CUDAICA (Raimondo et al., 2012), applied to continuous data to decompose it into source-resolved activities. Then, epochs were created using a time window of 3, −1.5 to 1.5 s, with respect to the red dot onset of the VSTS task (**Figure 2A**). Epochs with artifacts in specific channels were removed using an EEGLAB automated method based on extreme values of potential, data improbability and potential kurtosis (Delorme et al., 2007).

The selected epochs for the analysis were 90 epochs for the correct switches on Rule 3 (Rule 3 required subjects to switch back and forth between rules 1 and 2 every two trials, called Switch) and 90 epochs for correct answers on non-switch trials on Rule 3.

Envelopes of the ERP differences were visualized in order to identify the time windows containing the greatest ERP differences between groups. ERP envelopes were calculated using a (2 × time points) matrix whose rows represent the most positive and negative value, of all channels, at each time point. The sedentary group was contrasted with each of the active groups (TC, MEDe and AER) in the time window between −0.3 and 1 s. A first time window between 0.1 and 0.3 s showed the more evident differences and a second time window between 0.3 and 0.6 s revealed more subtle differences (**Figure 3A**). The ERP envelopes *per se* do not indicate the sources or brain regions generating the differences. Thus,

[1]https://sccn.ucsd.edu/wiki/Artifact_Subspace_Reconstruction_(ASR)

TABLE 1 | Anatomical information by Domains (BA, Brodmann Area; Prob, probability; R, right; L, Left).

	Brodmann Areas			**Anatomical Areas**	
Domains	**Area**	**Prob.**	**Description**	**Area**	**Prob.**
1.- Superior Frontal	BA 6	0.42	Premotor and Supplementary Motor	L Superior Frontal Gyrus	0.33
	BA 31	0.15	Primary Motor	R Superior Frontal Gyrus	0.25
	BA 24	0.13	Primary Somatosensory	L Precentral Gyrus	0.14
	BA 4	0.09	Somatosensory Association	L Postcentral Gyrus	0.05
	BA 3	0.06			
	BA 5	0.06			
2.- Secondary Visual (V2)	BA 18	0.50	Secondary Visual (V2)	Cerebellum	0.48
	BA 17	0.26	Primary Visual (V1)	R Lingual Gyrus	0.15
	BA 19	0.14	Associative Visual (V3)	L Lingual Gyrus	0.11
	BA 30	0.06		R Inferior Occipital Gyrus	0.10
				R Middle Occipital Gyrus	0.06
3.- L Anterior Cingulate	BA 24	0.50		**L Cingulate Gyrus**	0.33
	BA 23	0.42		L Caudate	0.27
	BA 32	0.07		R Cingulate Gyrus	0.17
				L Superior Frontal Gyrus	0.08
				R Caudate	0.07
				Brainstem	0.05
4.- R Superior Parietal	BA 7	0.24	Somatosensory Association	**R Superior parietal Gyrus**	0.39
	BA 5	0.19	Somatosensory Association	R Postcentral Gyrus	0.30
	BA 4	0.17	Primary Motor	R Precentral Gyrus	0.15
	BA 31	0.12	Primary Somatosensory	R Supramarginal Gyrus	0.07
	BA 3	0.12	Spatial and Semantic Processing		
	BA 40	0.10			
5.- R Posterior Parietal	BA 39	0.30	Auditory Processing	**R Angular Gyrus**	0.33
	BA 31	0.16	Associative Visual (V3)	R Middle Occipital Gyrus	0.25
	BA 37	0.12		R Superior Parietal Gyrus	0.18
	BA 22	0.09		R Middle Temporal Gyrus	0.09
	BA 19	0.07			
	BA 30	0.06			
6.- R Anterior Cingulate	BA 24	0.43	Premotor and Supplementary Motor	**R Cingulate Gyrus**	0.20
	BA 32	0.37		R Caudate	0.17
	BA 6	0.08		R Middle Frontal Gyrus	0.16
	BA 33	0.06		L Cingulate Gyrus	0.13
				R Superior Frontal Gyrus	0.10
				R Inferior Frontal Gyrus	0.08
				L Superior Frontal Gyrus	0.05
				L Caudate	0.05
7.- R Precentral	BA 4	0.29	Primary Motor	R Precentral Gyrus	0.52
	BA 3	0.26	Primary Somatosensory	R Postcentral Gyrus	0.27
	BA 6	0.21	Premotor and Supplementary Motor	R Superior Frontal Gyrus	0.09
	BA 40	0.10	Spatial and Semantic Processing	R Supramarginal Gyrus	0.05
	BA 2	0.06	Primary Somatosensory		
	BA 5	0.06	Somatosensory Association		
8.- Associative Visual (V3) R	BA 19	0.42	Associative Visual (V3)	Cerebellum	0.39
	BA 37	0.31	Secondary Visual (V2)	R Inferior Occipital Gyrus	0.32
	BA 18	0.18		R Lingual Gyrus	0.09
				R Inferior Temporal Gyrus	0.08
				R Fusiform Gyrus	0.06
				R Middle Occipital Gyrus	0.06
9.- R Anterior Cingulate	BA 24	0.34	Inferior Insula	R Caudate	0.30
	BA 32	0.15	Pars Triangularis Broca's Area	R Cingulate Gyrus	0.17
	BA 33	0.15		R Middle Frontal Gyrus	0.15
	BA 13	0.13		R Putamen	0.08
	BA 47	0.13		R Middle Orbitofrontal Gyrus	0.07
	BA 45	0.08		R Inferior Frontal Gyrus	0.06
				R Insular Cortex	0.06
10.- L Posterior Parietal	BA 40	0.49	Spatial and Semantic Processing	L Angular Gyrus	0.70
	BA 39	0.45	Associative Visual (V3)	L Supramarginal Gyrus	0.26
	BA 19	0.06			
11.- L Superior Frontal	BA 10	0.42		L Superior Frontal Gyrus	0.41
	BA 11	0.30		R Superior Frontal Gyrus	0.15
	BA 32	0.28		L Middle Orbitofrontal Gyrus	0.13
				L Gyrus Rectus	0.13
				L Middle Frontal Gyrus	0.11
				R Gyrus Rectus	0.07

Bold font indicates brain domains and their most probable location associated with attentional control and executive functions that are further analyzed in the result section.

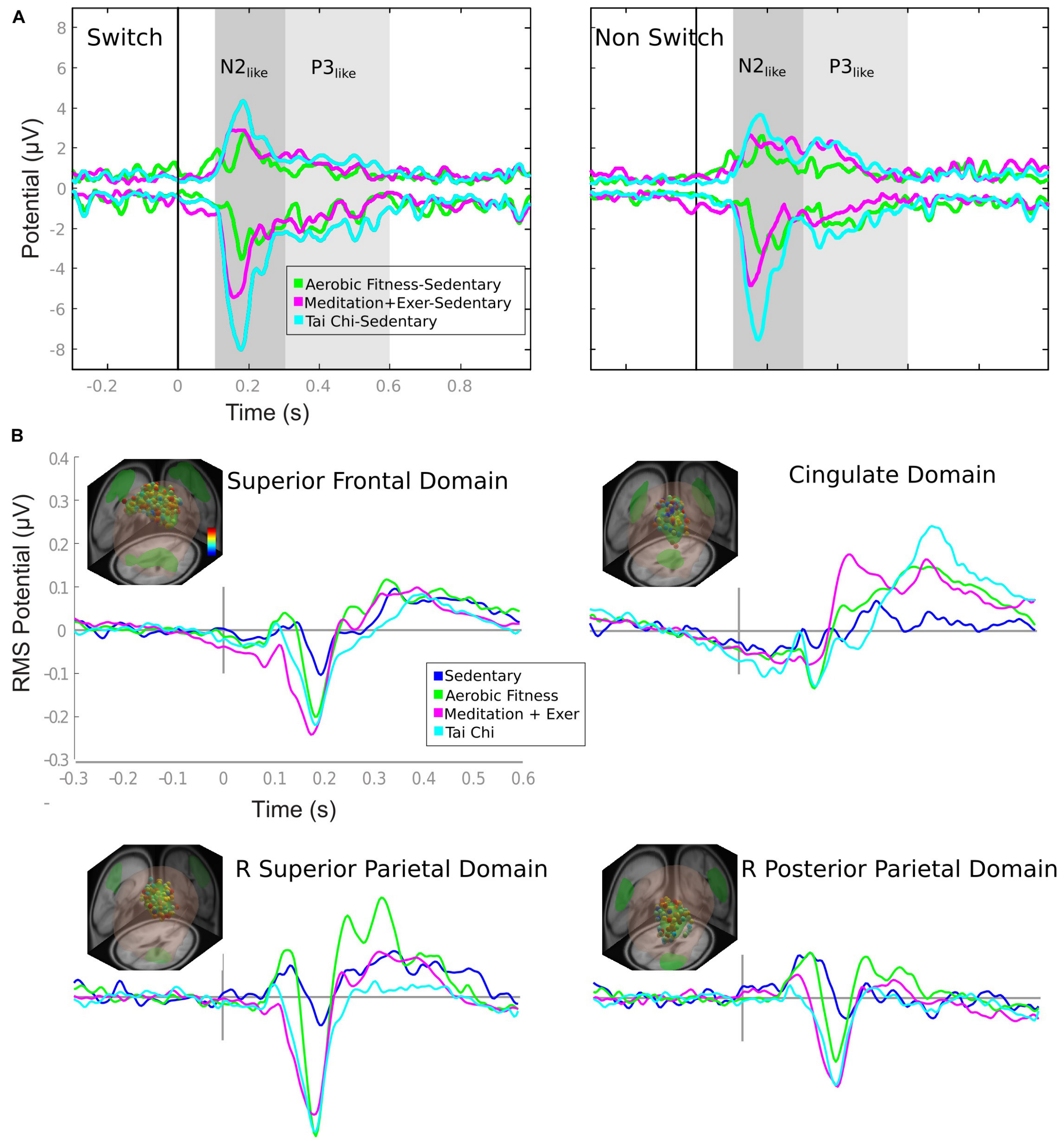

FIGURE 3 | ERP envelopes by group comparison and domain ERPs by group. **(A)** ERP envelopes in 1 s after stimulus presentation, contrasting active groups against sedentary group. The colored lines represent the subtraction showed in the legend. Gray shaded areas represent the time window considered for the ERP comparison of **Figure 5**. **(B)** Each domain contains the information of: location (e.g., superior frontal domain) (R, right; L, left); representative dipoles with colored dots related to a color bar with the probability of belonging to the domain (from 0 [blue] to 1 [red]); and ERP activity of switch epochs is in colored lines matched to the group legend (Sedentary to Tai Chi).

further source-resolved ERP analysis was performed. In order to estimate the brain sources contributing to the differences depicted by the envelope of the ERP difference, we performed an estimation of equivalent current dipole locations using a Boundary Element Model of Montreal Neurological Institute (MNI) head model with the EEGLAB dipfit plugin (DIPFIT[2]). Dipoles were then clustered in brain sources with the methods explained in the next section. ERPs were estimated for each brain source identified in the cluster analysis. In order to statistically explore the differences visually detected with envelopes, a time window from −0.3 to 0.6 s was used, corrected with a baseline from −0.3 to 0 s, with the polarity corrected by topoplots, filtered below 30 Hz and then averaged across data trials.

[2]http://sccn.ucsd.edu/eeglab/dipfittut/dipfit.htmlold

Clustering of Independent Components Dipoles

The clustering method used in this study determined the similarities between subjects, by conditions and groups. Correct responses for switch trials (transitions from the congruent to incongruent instruction and vice versa) and non-switch trials from Rule 3 blocks (**Figure 2B**) were analyzed. The Measure Projection Toolbox (MPT)[3] (Bigdely-Shamlo et al., 2013), was used to cluster brain dipoles from all subjects (**Figure 2C**). The MPT uses a template brain space grid of voxels of 8 mm (here MNI). Each voxel receives a probability of a representative ERP activity and location from the dipole information. To get the spatial domains - or probable location of the source-resolved activity—MPT clustered the brain subspace based on the correlation between ERPs of dipoles in nearby locations (**Figures 2C,D**).

The parameters used were a correlation threshold of 0.9 with a p-value less than or equal to 0.05. To increase the robustness of the results, measure projection analysis (MPA) was applied to 2,000 surrogate data with a false discovery rate (FDR) correction, resulting in a final p-value threshold less than or equal to 0.012. Furthermore, a three-dimensional Gaussian location error was considered in the location estimation. This error was equal to 12 mm with 3 standard deviations (3 6mm).

Finally, we selected the brain domains that had almost all the participants by group (greater than 85% of the participants by group), which resulted in the inclusion of areas related to executive functions previously reported during switching paradigms.

Participants Features, Behavioral, and ERP Statistics

All the statistics were analyzed in RStudio [RStudio Team (2016). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA, United States][4]

Participants features (Age, Education years, VO2max, BMI and self-reported training hours) were compared between groups using analysis of variance (ANOVA) with Sidak adjustment as a *post hoc* test (**Figure 1**).

Participant behavioral scores and ERP time windows were compared using multivariate analysis of covariance (MANCOVA) with Age, Education years, VO2max and BMI as covariables and group as the predictor and sex as cofactor. For the pairwise comparisons, we used a *post hoc* Sidak adjustment. We analyzed two ERP time windows as the area under the curve (**Figures 3A**, **4**). The first-time window was between 100 and 300 ms after the stimulus presentation (characterizing the N2-like wave in frontal and parietal domains), and the second time window was between 300 and 600 ms (characterizing the P3-like wave in the cingulate domain).

To visualize the nature and dimensionality response variation of the predictor (Group), cofactor (sex) and covariables (Age, Education years, VO2max and BMI) in the MANCOVA model we use heplot R function[5]. This function plots ellipses representing the hypothesis and error sums-of-squares and products matrices for terms and linear hypotheses in a multivariate linear model (**Figures 5C**, **6B**).

Finally, to visualize the variables without the influence of the group discipline factor we computed a K-Means clustering (with 4 expected groups) for the behavior using the Switch cost and Switch RT variables, and for a relation Behavior-EEG using Switch cost and the N2-like-area from right superior parietal domain (with the strongest group differences in MANCOVA). Then we contrasted the predicted cluster with the participants by groups, counting them in each predicted cluster (**Figures 5B**, **6A**).

RESULTS

Group Variables Comparison

Here we provide group contextual variables that inform our interpretation of the neural results, including age, education years, VO_2max, BMI, and self-reported hoursc of practice (**Figure 1**).

There were no significant differences in age between groups. The Tai Chi (TC) group had higher BMI compared to the Meditation + Exercise (MEDe) and Aerobic fittness (AER) groups (p = 0.005 and p = 0.017, respectively). The Sedentary (SED) group had higher BMI than the MEDe group (p = 0.033).

The SED group had lower VO_2max than the AER and MEDe groups (respectively $p < 0.001$, p = 0.001). The TC group had lower VO_2max than the AER group (p = 0.009).

The SED group had fewer education years than the MEDe (p = 0.003) and TC groups (p = 0.036).

With respect to sex, the MEDe and AER groups were similar in terms of the number of males and females, but the TC group had more males, and the SED group had more females.

Self-reported practice of TC, MEDe, and AER regimens showed TC practitioners reported significantly higher TC practice than the other three groups (MEDe, AER, SED, p = 0.002, p = 0.003, and p = 0.004, respectively), MEDe reported significantly higher meditation practice than the other three groups (TC, AER, SED, p = 0.002,p = 0.002,p = 0.004, respectively), and AER reported a similar amount of aerobic exercise compared to TC practitioners and MEDe, but a significantly greater amount of aerobic practice compared to SED (p = 0.021) (**Figure 1**).

In summary the SED group showed worse physical condition, fewer education years and training hours as expected; however, they were similar to the TC group on BMI and VO_2max.

Performance on the Executive Attentional Task

When comparing the performance on the attention switching task for the four groups, corrected only for Age, it was found

[3]http://sccn.ucsd.edu/wiki/MPT

[4]http://www.rstudio.com/

[5]https://rdrr.io/cran/heplots/man/heplot.html

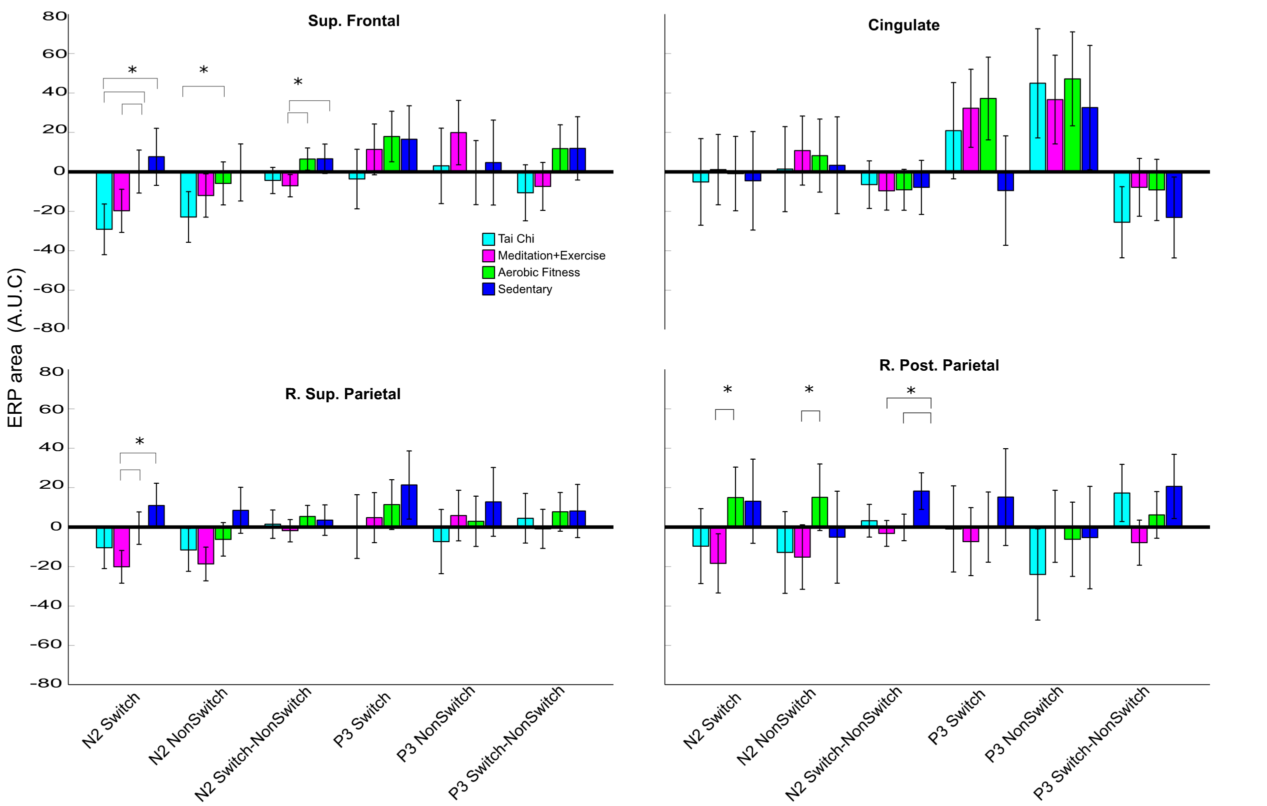

FIGURE 4 | Time-window (N2-like and P3-like area) differences between groups by domains and conditions. Each subfigure represents the average area under curve of N2-like (100–300 ms) or P3-like (300–600 ms) by group per domain and conditions. The conditions are switch trials from rule 3, non-switch from rule 1 and a subtraction of both, shown in the ticks of the X axis. The error bar represents the confidence interval at 0.95. Asterisks show a significant difference ($p < 0.05$) between the group connected by brackets.

that the Tai Chi and Meditation plus exercise groups showed significantly faster switch RT than the SED group (TC $p < 0.001$, MEDe $p = 0.001$, AER $p = 0.026$). The percent local switch costs showed with similar results, except for the AER group (TC $p = 0.001$, MEDe $p = 0.006$, AER $p = 0.446$).

However, when the comparison between groups was corrected for Age, Education years, VO_2max and BMI as covariables and sex as cofactor (**Figure 5A**), results showed that only the TC group had faster switch RT than the SED group (TC $p = 0.010$, MEDe $p = 0.714$, AER $p = 0.936$). In addition, percent local switch-costs were significantly smaller only for the TC group compared to SED (TC $p = 0.043$, MEDe $p = 0.464$, AER $p = 0.987$). This attention efficiency proxy (switch cost) was not statistically different between the TC and MEDe and AER ($p = 0.863$ and $p = 0.164$, respectively), and the AER was not statistically different from the SED group ($p = 0.982$).

Figure 5B shows that SED participants (blue dots) differed on switch costs and switch reaction times from all the other disciplines, whereas TC participants had better performance with less data dispersion (light blue dots) compared to MEDe and AER participants. The K-means clustering for the four groups showed that most of the people with the poorest performance (higher switch costs and higher switch RT) belong to the SED group (**Figure 5B**, gray ellipse), the people with the better performance belong to the TC and MEDe groups (yellow and black ellipse), while people from the AER group had an intermediate performance, most of the people in this group are contained in the brown and black clusters (see the legend C [T,M,A,S] of predicted cluster in **Figure 5B**, indicating number of participants in each cluster by group).

To evaluate the potential influence of Age, Education years, VO_2max, and BMI on reaction times and switch costs, we performed a heplot to show the MANCOVA results (**Figure 5C**) contrasting these variables with the predictor (group discipline). Discipline groups and Age had the main and the only significant effect size in the model (Partial Eta Square = 0.293 and 0.301 respectively), where older people tended to perform better, with slower Switch RTs (less effect on switch costs. Years of education also appeared as a positive predictor of performance, but this was not significant (Partial Eta Square = 0.087). The BMI and VO_2max factor had less influence in the model (Partial Eta Square = 0.029 and 0.002 respectively). Sex as cofactor indicates that gender was not correlated with performance, having a small influence compared to the Discipline factor (Partial Eta Squared = 0.040). Other combined effects in the model such as Discipline-Age or Gender-BMI did not have significant effects. The combined Gender-Age effects showed the smallest non-significant influence (Partial Eta Squared = 0.121).

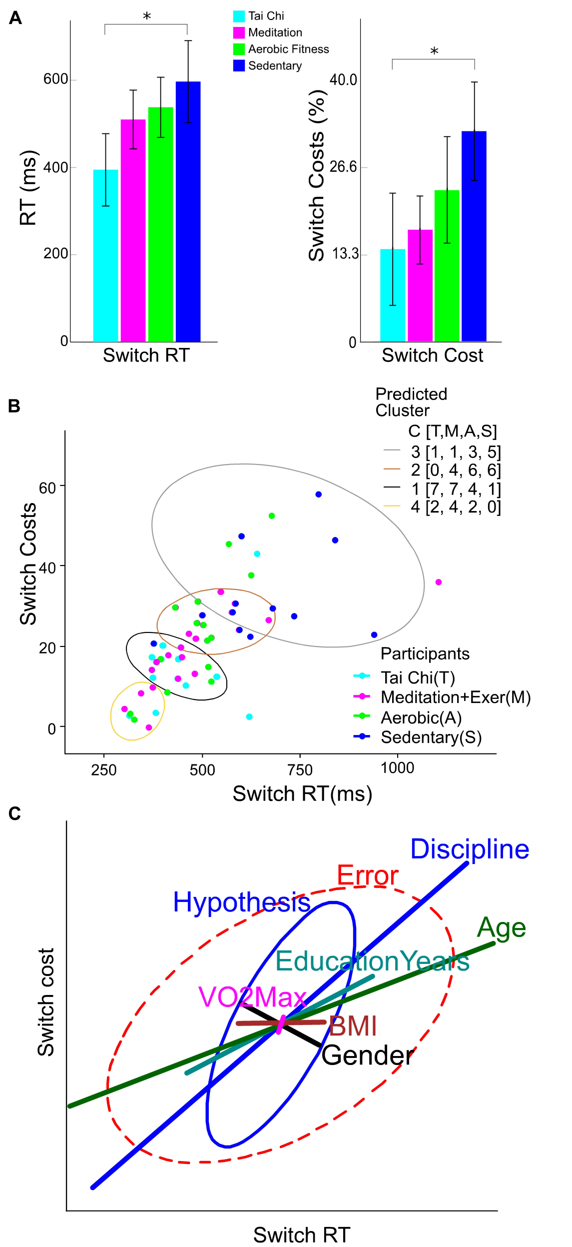

FIGURE 5 | Behavioral performance, clusters and variables weight in switching performance. **(A)** Reaction times (RT) in switch trials (left Y axis), and switch costs (right Y axis) by group discipline. The error bar represents the confidence interval at 0.95. Asterisks show a significant difference ($p < 0.05$) between the group connected by brackets. **(B)** K-Mean clusters of Switch reaction time and Switch cost. The legend labeled as Participants colored by group, light blue for Tai Chi (T), light red for meditation + exercise (M), green for Aerobic fitness (A) and blue for Sedentary participants (S). The legend labeled as Predicted Cluster contain the colors of ellipses that shows the output of participants by cluster number from 1 to 4. Additionally contain a counting of participants by group in C[T,M,A,S]. **(C)** Ellipses represent the hypothesis and error effects of the MANCOVA model and its orientation; the relation between variables showed in the x and y axis. The ellipse length represents the effect size in the corrected model, its width represents the data dispersion. The line length in colors represents the effect of the difference factor and covariables in the corrected model. The line orientation represents the relation between x and y variables.

Brain Domains

The clustering algorithm showed 11 brain domains involved in the performance of the switch task. The probable location of each domain is shown in **Table 1**, calculated based on the average location of each dipole within the domain's MNI brain space. Within the domains revealed by MPA, there were three domains located close to or in the primary visual and motor areas and the visual associative area, and eight domains with probable location in the superior frontal, anterior cingulate, and posterior parietal regions. However, some domains did not show activation in all subjects. Thus, we only analyzed domains that were active in at least 85% of participants per group, resulting in four domains that were subjected to further analysis: domains 1, 3, 4, and 5 (**Table 1**). Coincidently the brain location probability of these domains are associated with areas of attentional control and executive functions (Petersen and Posner, 2012), indicating that executive attentional network components were activated in all four groups.

Furthermore, we explored how these domains were involved in the processing of switch and non-switch events for each group.

Executive Attention Brain Domains Contributions to Channels ERP

The ERP envelopes of the SED group (maximum and minimum voltage from all channels in time) were contrasted against each of the exercise groups for switch and non-switch conditions. All comparisons – TC minus SED, MEDe minus SED, and AER minus SED – revealed that the greatest differences happened between 0.1 and 0.3 s and between 0.3 and 0.6 s (shaded areas in **Figure 3A**). The ERP waveform for these domains resembled the N2 component (Moore et al., 2012); therefore, we will refer to this waveform as the N2-like ERP. All three aerobic and combined regime training groups showed a positive modulation that resembled a P300. Traditionally the P3 is reported to have fronto parietal sources (Bledowski et al., 2004; Volpe et al., 2007). Our results showed the Anterior Cingulate Cortex as a possible source for this waveform, which has also been shown in other studies (Bledowski et al., 2004; Volpe et al., 2007). Thus, we will refer to this waveform as the P3-like ERP. Statistical differences within these time windows are reported in **Figure 4**.

The source ERP activity seen in the four brain domains included in the analysis and shown in **Figure 3B** (only switch trials are shown) explain around 85% (84.1–89.3%) of the variability observed in the channels, with the superior frontal and parietal domains accounting for most of the variability in all groups.

N2-Like and P3-Like ERP Differences: Controlling for Covariates

In the behavioral results section, we described how age and years of education contributed to the behavioral differences. Thus, it is necessary to investigate how much of the source ERP differences are explained by our main predictor Group Discipline, with Age, Educations years, VO_2max and BMI as covariables, and sex as

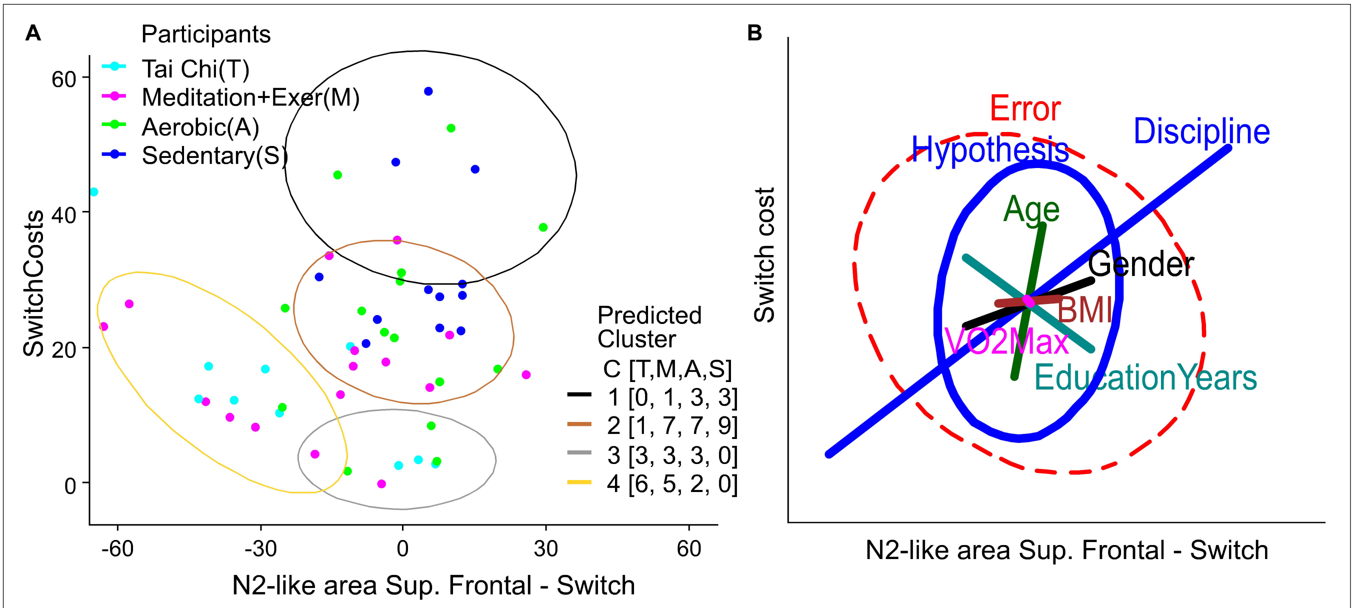

FIGURE 6 | Clusters and variables weight in Behavior-ERP relationship. **(A)** K-Mean clusters of switch cost and N2-like of right superior parietal domain. The legend labeled as participants is colored by group, light blue for Tai Chi (T), light red for meditation + exercise (M), green for Aerobic fitness (A) and blue for Sedentary participants (S). The legend labeled as Predicted Cluster contains the colors of ellipses that show the output of participants by cluster number from 1 to 4. Additionally, it contains a counting of participants by group in C [T,M,A,S]. **(B)** Ellipses represent the hypothesis and error effects of the MANCOVA model and its orientation, with the relation between variables shown in the x and y axis. The ellipse length represents the effect size in the corrected model, its width represents the data dispersion. The line length in colors represents the effect of the difference factor and covariables in the corrected model. The line orientation represents the relation between x and y variables.

cofactor. Thus, we used a multivariate analysis of covariance (MANCOVA), comparing N2-like and P3-like ERP modulations, and we used the area under the curve (AUC) as an index of the ERP amplitude. We included three conditions for the ERP comparisons: (1) Switch, (2) non-Switch and (3) its difference (Switch-Non-Switch). The difference between switch and non-switch was calculated to represent a neural estimation of switch costs or a normalized representation of switch trials. The analysis was performed separately for the main ERP domains (superior and posterior parietal, frontal, and cingulate domains shown in **Figure 3B**).

We will describe the results in three subsections, to clearly report how aerobic only or combined aerobic plus mental regimes affect neural processing during an attention switch task: (1) First, we describe whether a combined mental-physical training program or an aerobic regime showed any differences over a SED regime alone. (2) Then we describe the difference in combined mental-physical training over physical training alone. (3) Finally, we report ERP differences between the TC and MEDe groups. The ERPs by group are shown in **Figure 3B** and the statistical results are shown in **Figure 4**.

(1) Physical/mental activity vs sedentarism. In general, the SED group showed the smallest ERP amplitudes across brain domains. The superior frontal, right superior parietal, and right posterior parietal domains showed greater amplitudes within the N2-like time window, 0.1–0.3s, for the three training groups compared to the SED group (**Figure 3**). Most of the differences seen in the N2-like ERP remained significant after correction for multiple comparisons. **Figure 4** shows that the TC group had a greater N2-like ERP negativity for the Switch trials relative to the SED group (p = 0.002) in the superior frontal domain. Additionally, in the right superior parietal domain, the MEDe group showed a greater N2-like ERP negativity for the Switch trials compared with the SED group (p = 0.003). The MANCOVA also revealed that in the posterior parietal domain, the MEDe and AER groups differed from the SED group (respectively, p = 0.004 and p = 0.002) in terms of the Switch minus non-Switch difference, whereas in the superior frontal domain only the MEDe group differed from the SED group (p = 0.009) for the Switch minus non-Switch difference. Therefore, all discipline groups (TC, MEDe and AER) differed from the SED group in the N2-like ERP and domain. For the P3-like time window, between 0.3 and 0.6s, the most noteworthy difference was observed in the cingulate domain, where the aerobic and combined regime training groups showed a positive modulation that resembled a P3, which has been associated with greater top-down control during an attentional task (Pontifex et al., 2009), whereas this modulation was absent from the SED group (**Figure 3B**). However, differences in the P3-like ERP did not survive multiple corrections.

(2) Combined Physical/mental activity vs Aerobic exercise. The N2-like ERP began earlier and was more negative for the MEDe and TC groups (**Figure 3B**) compared to the AER group, across the superior frontal gyrus, right superior, and right posterior parietal domains. The MEDe group had significatively larger N2-like ERP negativity in the Switch condition compared

to the AER group in the superior frontal gyrus (p = 0.040), right superior parietal (p = 0.007), and right posterior parietal (p = 0.007) domains. The MEDs group also showed a greater N2-like ERP negativity for the Non-Switch trials relative to the AER group, but only in the right posterior parietal domain (p = 0.049). In contrast, the differences between the TC and the AER groups were significant only for the superior frontal domain, for both the switch (p = 0.002) and non-switch (p = 0.023) N2-like ERPs, with the TC group showing greater negative modulations (**Figure 4**). The Switch minus non-Switch difference between combined regimes and the AER group was only significant in the superior frontal domain for the MEDe group (p = 0.006), which showed greater negativity relative to the AER group. Therefore, even when both combined regimes, TC and MEDe, showed significatively greater N2-like negativities over the AER group, it was the MEDe group that most consistently differed from the AER group across domains and conditions.

(3) Differences between combined regimens (MEDe vs TC). In general, these groups showed similar activations in all executive domains. The parietal domains did not show any difference between these two groups, but some differences were observed in the frontal and cingulate domains. However, none of these differences resulted significant after correction for multiple comparisons (**Figure 4**).

In summary, (1) the differences between a combined mental-physical training program or an aerobic regime compared to the SED group were reflected in a larger negative amplitude of the N2-like component in the superior frontal and posterior parietal domains (2) The differences between following a combined mental physical regime in relation to a pure aerobic regime were mainly seen in the superior frontal domain, with some significant differences between the TC and AER groups in the parietal domains, with a more negative N2-like waveform for the combined regime groups. Moreover, (3) the differences between both combined regimes were not significant. Finally, it was the Switch condition in the superior frontal domain that showed most the group differences.

N2-Like ERP Differences: Factoring Out Age, Education Years, VO_2max, and BMI

In order to clearly report how much of the significant results reported above can be explained by Group Discipline, we are here indicating the effect size of each of the predictors included in the MANCOVA model. The results confirmed that the significant effects we found were mainly explained by the Discipline (Partial Eta Squared < 0.538) which people practiced: SED, AER, MEDe, or TC. Also, BMI had a significant influence (Partial Eta Squared = 0.264). Another important influence but with lower effect size was the sex of the participants (Partial Eta Squared = 0.196), Education Years (Partial Eta Squared = 0.092), Age (Partial Eta Squared = 0.228 and VO_2max (Partial Eta Squared = 0.144) had small influences on the results reported above. The factor Discipline also was a significant predictor of the model when combined with age and VO_2max: Discipline-Age (Partial Eta Squared = 0.524), Discipline-VO_2max (Partial Eta Squared = 0.441), as well as the factor Gender combined with BMI (Partial Eta Squared = 0.305). Thus, even though Disciple seems to be the main predictor it is important to take into account the multifactorial variables that can influence cognitive performance when interpreting the current results and how they combine to explain executive attention behavioral and neural outcomes.

Relationship Between N2-Like ERP and Behavior

Finally, to generate a combined model from Behavior and EEG we performed a K-means cluster analysis (**Figure 6A**) and produced a MANCOVA model (**Figure 6B**) based on Switch Costs, as the behavioral variable, and the N2-like ERP area under the curve (AUC) for the Switch trials, as the neural variable. We used the Switch ERPs from the superior frontal domain, because it was there that all the groups showed significative differences (**Figure 4**, top-left panel).

Figure 6A shows that most of the TC and MEDe participants had lower switch costs with a larger negative N2-like AUC (light blue and purple dots are mostly located within the brown and yellow clusters, respectively). Note that the larger a negative number is on the x-axis the larger is the ERP negativity (see **Figure 4** top-left for AUC and **Figure 3B** for ERP waveforms). In contrast, SED participants showed higher switch costs associated with smaller and more positive N2-like AUC values (blue dots are mostly located around zero or slightly toward positive values). All SED participants were contained within the higher Switch costs clusters (**Figure 6A, black** and **brown** ellipses). Also, the cluster containing participants with lower performance (black ellipse), have mainly SED and AER participants and only one participant from the MEDe group. Note that N2-like AUC values close to zero mean that the negative deflection of the N2-like ERP was very small (as shown in **Figure 4** top-left and **Figure 3B**). Similar to the behavioral results, people belonging to the AER group (green dots) showed intermediate values (**Figure 6A, brown** and **gray** ellipses). See the legend C [T,M,A,S] of the predicted cluster in **Figure 6A**, indicating the number of participants in each cluster by group. These results suggest a better switching performance was associated with greater negative N2-like ERPs for most of the participants.

To evaluate the potential influence of Age, Education years, VO_2max, and BMI on the relationship between switch costs and the N2-like AUC, we show the MANCOVA results in a heplot. Similar to the behavioral results, the model shows that Discipline had the greatest significant effect (Partial Eta Squared = 0.675), followed by Age (Partial Eta Squared = 0.383) (**Figure 6B**). As previously reported, there was no significant difference in age across groups (**Figure 1**). Thus, it is unlikely that age alone explains the relationship between Switch Costs and N2-like ERPs. The other variables only had a moderate influence and were non-significant in the model; BMI (Partial Eta Squared = 0.260), sex (Partial Eta Square = 0.209) and Education years (Partial Eta Squared = 0.136). VO_2max had a smaller influence (Partial

Eta Squared = 0.083). Therefore, our analysis indicates that Discipline had the greatest effect on the relationship between attention behavior and N2-like ERPs. Nevertheless, a broader interpretation of these results is required, as the combination of factors also appeared as significant predictors in the model: Discipline-Age (Partial Eta Squared = 0.532), Discipline-VO_2max (Partial Eta Squared = 0.422) and Gender-BMI (Partial Eta Squared = 0.283), indicating that the combined effects of these factors is important.

DISCUSSION

The present study investigated behavioral and neural correlates underlying a switch-task paradigm across people who chronically adhered to different exercise disciplines, varying in the degree of physical and mental activity required to execute each discipline. We reanalyzed the results obtained by Hawkes et al. (2014a,b) including a different statistical approach to known confounders and using a source-resolved approach (ICA) that allowed us to describe brain sources for ERPs. In addition, we used a cutting-edge method to perform group analysis (Bigdely-Shamlo et al., 2013), to identify common brain source activations between groups. This approach reduces the risk of equating brain activity produced at different electrode locations. Furthermore, we explored source-resolved ERP activity, instead of the more conventional channel ERP analysis, and applied a time-window statistical analysis. We used a MANCOVA to probe group differences and how much of these differences could be attributed to our main predictor factor: Discipline. As far as we know, there are no previous studies that contrast differences between combined mental and physical training, as Tai-Chi (TC) or Meditation + Exercise (MEDe), compared to aerobic exercise only (AER) or sedentarism (SED) in healthy participants using these methods. Thus, our results indicate there is an additive effect of the combined practice of physical and mental exercise in terms of behavior and its neural correlates based on N2 area under the curve analysis. In addition, we confirmed the participation of brain areas associated with executive functions (frontal, parietal, and cingulate areas) as generators of ERP components previously associated with switching tasks. Particularly, the N2-like component of the Superior Frontal domain appears as the area that better differentiates the different groups. Interestingly, the ERP amplitude in this area (measured as area under the curve) correlated with performance, such that a greater N2-like area under the curve was associated with better performance. The MANCOVA test on switching performance and ERP waveforms revealed that activity type was the most relevant factor, with an important influence of age, educational years, and BMI with small effects of VO_2max and sex.

Effects of Exercise Discipline and Confounding Factors

Our results differentiated the benefits of physical and mental regimes compared to a sedentary regime on a demanding non-cued switch task and suggest that the practice of combined physical and mental exercise may confer additive benefits in terms of behavior and its neural correlates. Our initial behavioral analysis comparing the switch trial reaction times and switch costs for the four discipline groups, using only age as a covariate, indicated that TC and MEDe practitioners showed significantly lower switch costs and switch reaction times compared to SED individuals, while those who practiced aerobic activity alone were not significantly different from sedentary adults, similar to previous articles by Hawkes et al. (2014a,b). However, when the analysis was made more stringent by including educational years, VO_2max, body mass index (BMI) and sex, these differences remained significant only for the TC practitioners. These results indicate that for the MEDe group, other factors, such as educational years and reduced BMI, contributed to their smaller Switch Costs and RT, relative to the SED group. The MANCOVA results indicated that Discipline indeed was the factor that explained most of the behavioral results, however, age also appeared as a significant predictor. As reported earlier, there was no significant difference in age across groups (**Figure 1**). Thus, it is unlikely that age difference explains the group results. In addition, one could expect older participants to show decreased performance compared to younger ones, however, our results report the opposite, the group with better performance was the one that tended to be older (TC). Years of education also appeared as a positive predictor of performance, but this was not significant. The TC and MEDe groups had significantly more years of education relative to SED controls. However, they did not differ in years of education compared to the AER and they outperformed them. This indicates that years of education alone did not explain the difference between groups. In terms of sex, despite having a different ratio of females to males in each group (TC contained mostly males while SEDs were mostly females), sex as cofactor only had a small influence in relation to group differences, as revealed by the MANCOVA. In addition, there are no reports in the literature indicating differences by sex with respect to local switch costs (Grissom and Reyes, 2019). Therefore, it is very unlikely that sex could explain the group differences reported here. In conclusion, the factor most likely explaining the differences in behavior and neural activation during the task switch test is Discipline. Here, we would like to point out that our participants had a middle age range (44–65 years) that from the point of view of the hypothesis of adaptive brain capacity (Raichlen and Alexander, 2017), suggests that early lifestyle changes that include combined physical and cognitive activities can protect the brain structure and function during normal aging, thus can allow participants to mitigate symptomatic neurodegenerative processes. We agree with the mechanism underlying this hypothesis, that a combination of simultaneous exercise and cognitive engagement acts as a stimulus for maintaining brain capacity across the lifespan (Raichlen and Alexander, 2017), and it is likely that combined physical and mental disciplines (TC and MEDe) confer benefits to cognitive performance (more neural specific mechanisms for the difference between groups are discussed below). One might ask if a minimum of a 5-year training time period is reasonable to use in this research study based on the time the brain needs to reorganize attentional activation patterns in response to mental and physical activity programs. In fact, a number of studies have shown significant brain reorganization and structural changes in response to as little as 8 weeks of mental (see Gotink et al., 2016 for a review) or physical training (see Smith et al., 2010 for a review). Thus, 5-years would be enough to produce a behavioral and neural effect.

Active (Physical or Mental) Regime Over a Sedentary Regime: N2-Like and P3-Like

The SED group had the slowest switch RT and the highest switch costs compared to the three exercise groups, and mainly differed from the TC group as seen in the high dispersion of behavioral data in the MEDe and AER groups. This suggests there are benefits to cognitive performance if normally aging adults engage in any active exercise regimen or combined regimes compared to a generally sedentary lifestyle. But, what about the neural correlates associated with these behavioral results?

Greater N2 and P3 amplitudes have been reported in studies investigating exercise regimes, with some exceptions (Gajewski and Falkenstein, 2015). Hillman and colleagues compared young and older, active and sedentary adults and found larger midline P3 amplitudes in active subjects (Hillman et al., 2006). Tsai and colleagues found greater P3 amplitudes in older adults after aerobic and strength training acute exercise bouts as well as longer term interventions (Tsai et al., 2018, 2019). Similar results were also observed for longer term interventions comparing training in open skills which require more cognitive processing, like table tennis, to closed skills, like aerobic walking or bicycle riding (Tsai et al., 2017). Hawkes et al., 2014b reporting from the same data set observed reduced P3 amplitudes for the SED group. Our source analysis suggested that the most likely candidate to produce this difference was the anterior cingulate domain, however, without significant group differences. Usually, P3s are reported in parietal areas (Bledowski et al., 2004; Volpe et al., 2007), but some studies have also found this type of activity in the cingulate (Volpe et al., 2007; Malinowski et al., 2017). That is why we refer to this modulation as P3-like—however, in this more stringent analysis that included more covariables we did not find significant differences in the cingulate area nor in the P3-like amplitudes. Thus, with our analysis we could not replicate previous studies reporting P3 differences between groups.

In contrast, The N2-like ERP modulation was the one that more consistently showed differences across groups. In terms of the likely brain generator for the N2-like ERP modulation reported here, we found that the superior frontal and parietal cortices contributed to most of the variation in the time window of the N2-like ERP. Accordingly, the source-ERP associated with these brain domains showed clear negative modulations around 200 ms. This is in line with previous literature showing N2 activity in frontoparietal electrodes (Hsieh et al., 2014; Tarantino et al., 2016).

We observed that the SED group showed the smallest and most positive ERP amplitude around 200 ms compared to the exercise groups. This difference occurred in the superior frontal superior parietal and posterior parietal domains. The ERP waveform of these brain domains resembled the N2 component (Moore et al., 2012), which is associated with greater task-related attention or novelty (Luck, 2005). The N2 have been reported in other studies using task switch paradigms (Wylie et al., 2003; Hsieh and Liu, 2008; Gajewski and Falkenstein, 2015; Tarantino et al., 2016); however, the N2 reported in the current study was larger than that seen in previous studies. Accordingly, the greater N2 negativity we found for exercise disciplines is similar to those reported in studies comparing active with inactive individuals (Polich and Lardon, 1997; Pontifex et al., 2009; Taddei et al., 2012): one previous study of combined mental and exercise practice (Mindfulness Training Based Stress Reduction TM [MBSR]) compared to untrained controls using an emotional Stroop task reported differences in N2 amplitude between groups (Malinowski et al., 2017). Taddei et al. (2012) showed that N2 and P3 amplitudes in a Go-no Go task were larger in fencers (which is a physical activity with a cognitive component) vs. inactive controls and this effect was independent of age. Greater ERP amplitudes may be indicative of increased local synchronization of neuron fields in sources which are modulated by attentional processing. This suggests that maintaining an active physical or mental training regime compared to a sedentary lifestyle may provide benefits to early attentional processing of task stimuli and in the decision-making process. Overall, our results suggest decreased top-down activation in the parietal and frontal domains for the SED group during this visuospatial attentional task.

Combined Physical and Mental Activity Over a Pure Aerobic Regime: N2

In terms of the behavioral results, percent local switch costs and switch RT were not different for MEDe and TC practitioners compared to the aerobic group. However, our K-Means clustering analysis clearly showed that AER participants had an intermediate performance relative to combined regimes and SED people (**Figure 5B, black** and **brown** ellipses).

In terms of the neural correlates, we showed that both combined regimes, TC and MEDe, showed significantly greater N2-like negativities compared to the AER group. However, it was the MEDe group that most consistently differed from the AER group across domains and conditions. Also, ERPs for the TC group in the superior frontal domain differed from the AER group but not from the MEDe group. This suggests complex executive function was more efficient in combined regimen practitioners, but depending on the specific exercise regime, different brain areas may account for the differences reported. Thus, we provide the evidence suggesting that combined practice provides an additive effect. What kind of mechanisms are considered to be trained in the combined programs that are needed for switching tasks? Research suggests that the executive attention system is important for task-switch paradigms (Watanabe et al., 2013; Schneider, 2015). This is because the executive system needs to keep track of both the trial sequence, and when in the sequence one needs to switch task rules. The combined program gives not only physical training, which brings more blood to the brain, which has been shown to improve executive function (Guiney and Machado, 2013), but it also trains executive attention circuits through tasks requiring high degrees of focused concentration (Taren et al., 2017). Thus, the combined program improves executive attention in a two-pronged way, through both physical and mental training. A likely neural correlate of the improved performance is the greater N2-like ERP shown by TC and MEDe. Similar to what we discussed in the previous section, the increased N2 amplitudes in the right posterior parietal area may reflect greater top-down control during an attentional task, which allows better executive control and faster responses. Further, Switch costs and N2-like amplitudes showed a positive correlation as shown in **Figure 6B**.

The MANCOVA model based on switch Costs and the amplitude of the N2-like ERPs during the Switch condition for the superior frontal domain showed that a better switching performance was associated with greater negative N2-like ERPs for most of the participants. The most likely predictor of this correlation is Discipline; however, the combination of Discipline with Age and Physical condition (VO_2max) also accounted for part of the effect described above. Thus, it is important to interpret these results in the context of multiple factors that affect health, cognitive performance, and general wellbeing in people. Our results are in line with previous studies that suggest the advantage of practicing combined physical and cognitive training compared to physical activity alone (Anderson-Hanley et al., 2012; Barcelos et al., 2015; Eggenberger et al., 2015; Tsai et al., 2017, 2018). For example, Tsai et al. (2017) found that when comparing training in open skills which require more cognitive processing, than closed skills, the open skill training produced reaction time facilitation in switch and non-switch trials, while the closed skill training did not (Tsai et al., 2017).

Differences Between Combined Regimes

The combined regimens showed small timewise differences in the early stimulus processing time window in frontal and cingulate domains. However, no significant differences were found. These data suggest similarities in the neural processing of attentional information between the two combined training groups.

Brain Source Analysis and Selection of Brain Domains

The use of a brain source analysis increases the spatial resolution of the EEG analysis (Akalin Acar et al., 2013). However, it is still far from the resolution of spatial information revealed by imaging studies. In the following paragraphs, we will discuss our results in light of evidence from previous imaging studies.

The group analysis method used in this study allowed us to confidently compare the electrical activity produced by the same brain regions by group. Main areas for the switch ERPs were localized to the bilateral superior-frontal, bilateral anterior cingulate (ACC), and right superior, and right posterior parietal cortices. All these brain regions have been described as relevant for the performance of switch paradigms by previous neuroimaging research (Rushworth et al., 2002; Swainson et al., 2003; Brass and von Cramon, 2004; Brass et al., 2005). However, we did not find group differences in the ERP analysis for the cingulate domain and the area that most consistently showed differences between groups was the superior frontal domain. This is relevant because the prefrontal activity in a switching task probably reflects the ability to deal with multiple cognitive rules and to coordinate behavior according to these rules (Nyhus and Barceló, 2009).

The parietal domains were mainly responsible for differences between the MEDe and AER groups (effect of combined regime over a pure aerobic one). The Superior Parietal Domain (SPC) has been recently associated with visuospatial working memory tasks and is especially involved in the manipulation and rearrangement of information that it is necessary during switching trials (Koenigs et al., 2009). Also, the SPC has been associated with visual perception changes during bi-stable paradigms (Kanai et al., 2011) which is similar to the visuospatial processing required to perform the task switch paradigm used in the original study. These results suggest a superior parietal contribution to the speed of processing associated with the rule updating required to perform switch trials and this may be the particular top-down mechanisms by which MEDe performed better than AER. In addition, the Posterior Parietal domain (PPC) has long been studied in relation to attention, and previous studies have shown it contributes to switch task performance and the ability to shift attentional sets (Liston et al., 2006). The right PPC has been associated with the orientation of visuospatial attention toward salient features and with a bottom-up strategy to attend to retrieved memories (Seghier, 2012). In our task, the PPC area could have contributed to differentiating between rules during the switching (N2 area results) and between left and right stimuli during the trials (Hirnstein et al., 2011; Chen et al., 2012). Differences between MEDe and AER in this area suggest that the PPC mediates the additive effect of combined physical and mental disciplines.

Limitations

The original study recruited subjects from one county in Oregon, United States who fulfilled the requirement of practicing the different regimes (or being sedentary) for more than 5 years. This means causation cannot be established based on exercise practice by exercise type. Further, only the key variables known to explain exercise variance were included in the original study as dependent variables in order to document their association with executive function. Further, training quality, which could partially explain the differences seen between our groups was only evaluated through long-term training effects on VO_2max and BMI. We used these factors as cofactors in our MANCOVA analysis and showed that the main factor that explained ERP differences was group, over age, VO_2max, and sex ratio, which is what was seen in the original analysis. Further studies should include measures of depression and mental status, a balanced sex ratio for each group, blood pressure, smoking and drinking status, and nutrition to further document the effects of diverse variables known to affect human cognition, as well as long-term exercise training, on normally aging adult executive function. Additionally, longitudinal training studies comprising the variables above will provide clarity on which variables or combination of variables predict better executive function in normally aging adults.

Also, we tried to include the self-reported hours of meditation, TC, and aerobic activities in the MANCOVA analysis, but the effect size of these variables was close to 0 and also the correlation values (Pearson) with switch cost performance were below 0.2. This could be due to the retrospective report of practice hours not well reflecting the intensity and quality of the commitment or an over or under estimation of the real amount of practice.

The value used in the arg_burst parameter of clean raw_data function (5 standard deviations) during the EEG preprocessing was based on the parameters suggested in Mullen et al., 2015. However, new empirical results (Chang et al., 2020) suggest that a number in the range of 20–30 standard deviations should be used. 5 SD can be aggressive and lead to loss of brain information. Future research may use Chang et al. article as a guideline.

The Measure Projection Analysis used to cluster brain dipoles is a new tool that requires further theoretical and empirical development to provide a more insightful and quantitative interpretation of results. One possible limitation in using this method is known as "double dipping": MPA first uses ERP measures (in the case of the current study) to create consistent domains and then tests their differences across conditions, using the data twice. Circular analyses have been flagged in fMRI studies (Kriegeskorte et al., 2009; Vul et al., 2009). Unfortunately, to the date of this publication there are neither analytical nor empirical analyses that quantify the impact of this issue in MPA. We strongly believe that MPA is still a valid approach, first, because it is expected that ICs localized within a certain region naturally show correlated activation patterns, even without using the constraint of similarity of measures. Secondly, the number of ICs is orders of magnitude smaller than the number of voxels in fMRI studies, where circular analysis has been described. To increase robustness of our results we have applied MPA to 2,000 surrogate values at each voxel, with a resulting final p-value threshold less than or equal to 0.01. Nevertheless, future methodological studies should clarify the real impact of circularity using MPA. Furthermore, even though MPA is more data-driven than other clustering methods, it still requires parameters that are user-specified: local convergence value and maximum correlation value. There are no empirical studies that provide practical guidelines for choosing these parameters. It is a probabilistic approach; thus, neighboring domains can overlap, making interpretation challenging. Thus, there is no absolute certainty for source localizations. In addition, as far as we know, whether the assignment of brain activity to subcortical structures reveals actual deep-source or broad-surface-source activity has not been addressed in methodological studies. It is possible that the use of single subject models to represent brain sources can reduce the accuracy of deep source localization (Nunez et al., 2006). The source localization problem is, however, inherent to any source modeling and clustering method developed so far. Thus, caution is required when attributing brain activity to brain regions and, in particular to deep structures (as is the case of the ACC). For this reason, in this paper, we talk about the probable location of brain domains, rather than brain cortex, regions, or areas. Finally, longitudinal, carefully controlled training studies are needed to further identify brain regions active during executive function tasks in normal adult humans.

Conclusion

This study is one of a growing number of studies investigating combined physical and cognitive training benefits, including the development of new training-based interventions to delay, mitigate, or eliminate dementia and cognitive impairment. Based on a robust methodology for analysis of brain clustering and multiple comparison between groups with covariables and cofactors, we showed that there is a linear correlation mainly explained by training Discipline, where sedentary people showed the lowest performance, Tai-Chi and Meditation + exercise practitioners showed the better performance and most aerobic-only practitioners showed intermediate performance. Furthermore, performance was correlated with the amplitude of the N2-like ERP negativity, particularly in the Superior Frontal brain domain. These results suggest that combine physical and cognitive activity (such as TC and MEDe) may offer benefits over performing aerobic exercise alone, to improve the executive attention network in healthy aging adults. We hypothesize that at a neural level this benefit is mediated by better early attentional processing of task stimuli. In addition, the importance of other cofactors (such as age and years of education) cannot be ruled out, due to the cross-sectional nature of our study. Thus, future experimental studies and longitudinal designs are needed to confirm the advantage of combined programs and understand the mechanisms that contribute to the cognitive improvements associated with these programs.

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 Oregon Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PB contributed to the conception, design, and interpretation of the data, drafting, revising, and approval of the work and is accountable for all aspects of the work. GC contributed to the analysis, interpretation of data, critical revision and approval of the work and is accountable for all aspects of the work. TH contributed the original data set and critically revised the manuscript and is accountable for all aspects of the work. IR-S contributed to critical revision and approval of the work and is accountable for all aspects of the work. MW contributed to the conception, design, and interpretation of the data of the work, and revised, approved and is accountable for all aspects of the work. All authors contributed to the article and approved the submitted version.

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Resting Theta/Beta Ratios Mediate the Relationship Between Motor Competence and Inhibition in Children With Attention Deficit/Hyperactivity Disorder

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Despite that previous studies have supported relationships between motor ability and inhibitory function, and between resting brain theta/beta power ratios (TBR) and inhibition in children with attention deficit/hyperactivity disorder (ADHD), little research has examined the mechanism within these relationships. The purpose of this study was to investigate whether TBR would mediate the relationship between motor ability and inhibitory function. A total of 71 children with ADHD were recorded resting electroencephalographic (EEG) data during eyes-open. Motor abilities were evaluated by Movement Assessment Battery for Children-2 (MABC-2) and inhibitory ability were assessed by a modified Eriksen's flanker task. The results of mediation analyses revealed that TBR could completely mediate the relationship between motor competence and response speed (indirect effect = −0.0004, 95% CI [−0.0010, −0.0001]) and accuracy (indirect effect = 0.0003, 95% CI [0.0000, 0.0010]) in the incongruent condition of the flanker task. This study suggests that TBR may be one of the mechanisms between motor ability and inhibition function in children with ADHD.

Keywords: ADHD, TBR, motor ability, interference, mediator

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is one of the most pervasive childhood developmental disorders and approximately 27% of children with ADHD suffer from deficits in inhibition function (Kofler et al., 2019). Inhibition refers to the ability to inhibit responses, which is associated with executive neuropsychological functions that appear to depend on it for their effective execution such as working memory, regulation of motivation, internalization of speech, and reconstitution (Barkley, 1997), as well as fine and gross motor abilities (Band and van Boxtel, 1999). Inhibitory dysfunctions typically result in long-term consequences as problems in mood regulation, family life, peer relationships, academic achievement and future prospects among children with ADHD (Youn et al., 2019). Although medication and behavioral treatments for ADHD symptoms are recommended, some potential side effects and costs often reduce their overall effectiveness (Rajeh et al., 2017) and thus making it important to explore lifelong adjunctive or alternative treatment options that may benefit children with ADHD. Based on this concern, factors associated with inhibition functions in children with ADHD and their mechanisms deserve further investigation.

For children with ADHD, problems of fine and gross motor skills, coordination skills, and motor control have been found to relate to inattentive or combined symptoms (Fenollar-Cortés et al., 2017). Therefore, deficits in motor competence are often accompanied by cognitive impairments in children with ADHD. Motor competence refers to the degree of proficiency in performing a wide variety of motor skills including both gross (e.g., jumping) and fine (e.g., manual dexterity or precision) motor skills as well as the underlying mechanisms including coordination, control, and quality of movement. There is extensive research examining potential relations between motor competence and inhibition functions in different populations. Recent research within typically developing children has reported a significant relationship between motor competence and response inhibition (Albuquerque et al., 2021), and children with typical development exhibit better inhibitory performance than children with motor impairments (Yu et al., 2020). Also, motor competence such as coordination associated with throwing and striking and hand dexterity could predict inhibitory performance at a Go/No-Go task in children with ADHD (Hung et al., 2013). Several intervention studies have identified beneficial effects of motor skill training programs on inhibition and attention in children with ADHD. For example, Verret et al. (2012) found that a 10-week ball games program (basketball and soccer) not only improved fitness and gross motor skills but also information processing and sustained auditory attention. Similarly, Pan et al. (2016) reported a 12-week table tennis exercise program improved motor skills (e.g., locomotor and object-control skills) and performance on tasks involving planning and inhibition. Furthermore, the relationship between motor competence and inhibition function appears to be causal since it has been shown that an 8-week coordination exercise program led to improved inhibition in kindergarten children (Chang et al., 2013). Previous research has indicated that common mechanisms associated with the cognitive deficits and motor difficulties of children with ADHD may involve several brain structures (Halperin and Healey, 2011) and neurotransmitter systems (Prince, 2008). Therefore, high levels of motor competence might contribute to enhanced inhibition via the restoration of normal functioning involving these brain areas and neurotransmitter systems.

Motor cortical regions of the frontal cortex are considered to be highly associated with the acquisition and/or consolidation of skilled motor behaviors, as well as rich dopaminergic pathways (Luft and Buitrago, 2005). Furthermore, by using a technique of transcranial magnetic stimulation, short interval cortical inhibition (SICI) evoked in motor cortex is significantly reduced in children with ADHD compared to typically developed children (Gilbert et al., 2011). Reduced SICI in motor cortex is viewed to correlate with the presence and severity of hyperactive impulsive behaviors in children with ADHD as well as with commonly observed delays in motor control. Therefore, the neural substrate of these motor delays and inhibition dysfunction may include mechanisms within or adjacent to the motor cortex. Given that children with ADHD are commonly featured by motor difficulties and inhibitory control deficits, the association between low motor competence and weak inhibition might be mediated by some stable and predisposed variables. A resting EEG indicator, theta/beta ratios (TBR), might be one of the mediators. Inhibition dysfunction in children with ADHD is identified to be resulted from cortical under-arousal (Clarke et al., 2001) as indicated by increased ratios of EEG slow waves to fast waves, such as TBR, during the resting state. Previous research has demonstrated a negative relationship between TBR and inhibition performance (Putman et al., 2010) and suggested that TBR may serve as a stable biomarker for inhibition in children with ADHD (Zhang et al., 2017). Moreover, in a randomized controlled trial, neurofeedback training aimed at reducing TBR resulted in reduced symptoms in children with ADHD (Janssen et al., 2016). Regarding the association between motor competence and TBR, previous research has found that children with ADHD show worse motor competence and higher TBR than typical development children (Huang et al., 2018). Based on maturational lag and hypo-arousal model, elevated TBR in children with ADHD is partly associated with delayed development of the brain's ascending reticular activation system that leads a disturbance in thalamus-cortical transactions (Saad et al., 2018). By using a sample of normal adult mice, the acquisition of motor skills has been found to induce synaptic modifications in the primary motor cortex in which the stabilization of motor thalamus can be enhanced (Hasegawa et al., 2020). Although little evidence has directly shown the causal relationship between motor competence and TBR, high levels of motor competence may contribute to develop more efficient thalamocortical pathways which may be reflected by reduced TBR. Therefore, it is postulated that a negative association between motor competence and TBR might be expected in children with ADHD.

While a positive relationship has been demonstrated between motor competence and inhibition in children with ADHD, there is limited research as to the underlying mechanism (Chang et al., 2013; Hung et al., 2013). Given that motor competence (Halsband and Lange, 2006), TBR (Chabot and Serfontein, 1996), and inhibition (Casey et al., 1997) all involve the frontal cortex and it is known that reduce in TBR may reflect improved inhibition, it is possible that the influence of motor competence on inhibition is mediated through the biological/physiological pathways reflected by TBR. Therefore, the main purpose of this study was to examine whether TBR could mediate the relationship between motor competence and inhibition in children with ADHD.

METHOD

Participants

A total of 71 children with ADHD (mean age = 9.90 ± 1.54 years) from local elementary schools in Taipei were included in this study (**Table 1**). They were referred by special education teachers

TABLE 1 | Demographic and physical characteristics of the participants.

Characteristics	Mean ± SD
Gender (boy: girl)	48:23
BMI (kg/m^2)	19.50 ± 1.5
ADHD type	
ADHD-I	30
ADHD-HI	5
ADHD-C	36

BMI, body mass index; ADHD-I, predominantly inattentive subtype; ADHD-HI, predominantly hyperactive-impulsive subtype; ADHD-C, combined hyperactive-impulsive and inattentive subtype.

and parents to participate in this study. Sample size was determined to ensure sufficient power by using power analysis software (G*Power 3.1). We set the following input parameters for using a linear multiple regression with alpha = 0.05, power = 0.80, effect size f^2 = 0.15 (medium), and 2 predictors. The resulting sample size specification was 68. Therefore, the current sample was shown to have a greater than 80% probability of detecting a medium size effect. Recruitment criteria were as follows: (1) aged between 8 and 12 years; (2) diagnosed by a pediatric psychiatrist as having ADHD based on the criteria of the fifth edition of the *Diagnostic and Statistical Manual for Mental Disorders* (DSM-5; American Psychiatric Association, 2013); (3) no co-morbid conditions, such as conduct/oppositional defiant disorder, autism spectrum disorders, or serious affective disorders; and (4) no history of brain injury or neurological conditions, such as epileptic seizures, serious head injuries, or periods of unconsciousness. In addition, the legal guardians of our participants confirmed the presence of the ADHD symptoms using the Child Behavior Checklist (CBCL), a component in the Achenbach System of Empirically Based Assessment (Achenbach and Rescorla, 2001). For the purpose of this study, only the items relevant to the assessment of ADHD were utilized. The average ADHD scale score for the participants in the current study was 67.18 ± 6.8. While the clinical cutoff score for a diagnosis of ADHD is above 70 (Achenbach and Rescorla, 2001), score ranging from 65 to 69 are considered clinically borderline. All participants were instructed to stop medications for at least 24 hours prior to the start of this study. Their parents completed a written assessment and gave informed consent. This study was approved by the Institutional Review Board of National Taiwan Normal University (201010HS001).

Measure

Motor Competence

This study used the Movement Assessment Battery for Children-2 (MABC-2) to assess participants' motor abilities, a test designed to identify and describe impairments in motor performance of children and adolescents 3 through 16 years of age (Henderson et al., 2007). The MABC-2 includes 3 subtests: manual dexterity (placing pegs, threading and drawing), aiming and catching (two handed catching and beanbag throwing), and balance (on-board balancing, walking heel to toe, and hopping). The three subsets of the MABC-2 were converted into standard scores, then transform to the percentile scores on these subsets. Although some items of the MABC might need to be adjusted in Asia-pacific countries (Chow et al., 2006), the reliability and validity of the MABC-2 are still fair based on a large sample of Chinese preschool children (Hua et al., 2013).

Inhibition

The Eriksen's flanker task was used to examine interference control and inhibition. The task included two types of trials. In 'congruent' trials stimuli consisted of a horizontal array of five arrows all facing in the same direction (i.e., <<<<< or >>>>>). In 'incongruent' trials, the central target arrow was flanked by two arrows on each side facing in the opposite direction (i.e., <<><< or >><>>). By replicating the protocol used in a previous study (Tsai et al., 2017), the flanking stimuli were presented as 3 × 3-cm figures, at a 2.87° visual angle, in the center of a computer screen, 60 cm from the participant, on a black background. Participants completed 5 blocks of 32 trials presented with equiprobable congruency and directionality. Left and right target arrows were presented with equal probability and were randomized within each block. Each trial began with a central fixation cross (+) for 1000 ms, followed by the presentation of the target stimulus in the center of the computer screen for 200 ms. A blank screen was then shown for 1500 ms. The next trial began after a response was made, or at the end of the response window, i.e., 1700 ms after the target stimulus presentation. Participants were instructed to respond to the central target arrow by pressing the keyboard letters 'V' (with their left index finger) or 'N' (with their right index finger) as quickly and accurately as possible, to indicate whether the stimulus presented pointed to the left or right respectively. Participants were allowed a one-minute break between blocks. The total duration of the task was approximately 12 min.

The behavioral performance measures including reaction time (RT) and accuracy (correct responses) were calculated in the congruent and incongruent trials, respectively. RT was defined as the interval between the onset of a stimulus and a response. Only RTs recorded from correct responses occurring within the response window (between 150 ms and 1000 ms) were included for subsequent analysis.

EEG Recording and Data Reduction

Electroencephalographic activity was recorded from 28 midline and lateral Ag/AgCl electrodes positioned according to the International 10–20 system using a NeuroScan Quik-Cap (Neuro Inc., Charlotte, NC, United States). Vertical electrooculogram (VEOG) was collected from electrodes placed above and below the left eye and the horizontal electrooculogram (HEOG) from the outer canthus of each eye. A ground electrode was attached to the middle of the forehead, and all electrodes were referenced to linked ears. Electrode impedance was kept below 10 kΩ. EEG and EOG were amplified with a bandwidth of DC-to-100 Hz. The sampling rate was 500 Hz. In addition, a 60-Hz notch filter was utilized during the data acquisition. Prior to data processing, EEG data were filtered using a band-pass cutoff of 1-30 Hz (12 dB/octave) and EOG corrected by an algorithm. The continuous EEG data were segmented into 2-s epochs. After a baseline correction and visual inspection for artifact, the cleaned EEG data were Fast Fourier transformed and subsequently ln-transformed. Power estimates were calculated using fixed frequency (4-7.5 Hz for theta and 13.5-25 Hz for beta) bands at the Cz site, which has been found to have the greatest ability to distinguish between ADHD and healthy controls (Monastra et al., 1999). Furthermore, the ratio coefficient of theta/beta was computed.

Procedure

Each participant came into the laboratory on a single occasion. The day before participants were reminded to avoid caffeine and food products containing alcohol. On arrival in the laboratory, participants were familiarized with the testing procedure as well as the laboratory environment. Written informed consent forms, as well as health and demographic questionnaires were provided to the accompanying adults. Participants were then asked to complete a test of motor competence, after which they were fitted with an electrode cap, and impedances and the quality of the EEG signal were checked. Then, sitting calmly in a comfortable chair with eyes open in a sound-attenuated testing room, EEG data was collected twice for one minute each. After these two EEG data collections, the participants then engaged in the flanker task.

Statistical Analysis

Descriptive statistics were computed, and Pearson correlation coefficients were estimated among motor competence (the MABC-2 score), the resting TBR, and inhibition indicators (RT and accuracy rate at the flank task). A bootstrapping method was performed using SPSS PROCESS Macro (Hayes, 2013) to examine if the resting TBR mediated the relationship between motor competence and behavioral performance of the flanker task in children with ADHD. The mediation analyses were conducted with 1,000 bootstrapping resamples to obtain bias-corrected 95% confidence intervals. All statistical analyses were performed using SPSS 21.0 with a significance level of 0.05.

RESULTS

Preliminary Analysis

As shown in **Table 2**, motor competence (the MABC-2 score) was negatively correlated with the TBR, RT in the congruent trials (C-RT), and RT in the incongruent trials (IC-RT), as well as positively correlated with accuracy in the congruent trials (C-ACC) and accuracy in the incongruent trials (IC-ACC). Regarding the subsets of the MABC-2, the percentile score of manual dexterity was negatively correlated with C-RT and IC-RT, as well as positively correlated with C-ACC and IC-ACC. The percentile score of aiming and catching was negatively correlated with the TBR and positively correlated with C-ACC. The TBR was negatively correlated with IC-ACC and positively correlated with C-RT and IC-RT. All significant levels reached at $p < 0.05$.

Mediation Analyses

The purpose of this study aimed to examine whether TBR could mediate the relationship between motor competence and inhibition in children with ADHD. A bootstrapping method was performed using SPSS Process Macro to conduct the mediation analyses. As shown in **Table 3**, the motor competence (independent variable) could significantly predict C-RT of the flanker task (dependent variable), and the resting TBR (mediator). Next, the resting TBR was a significant predictor of C-RT of the flanker task. While controlling for resting TBR, the result showed that the motor competence was still a significant predictor of C-RT of the flanker task. The results of the indirect effect based on 1000 bootstrap samples revealed that a significant indirect negative relationship between motor competence and C-RT of the flanker task was partially mediated by the resting TBR.

As shown in **Table 4**, the motor competence was significant predictors of C-ACC of the flanker task and the resting TBR. However, the resting TBR was not a significant predictor of

TABLE 2 | Correlations among Motor Competence, TBR, and Inhibitory Performance.

	1	2	3	4	5	6	7	8	9
1. MABC-2 (%)	-								
2. Manual dexterity (%)	0.71**	-							
3. Aiming & catching (%)	0.78**	0.36**	-						
4. Balance (%)	0.59**	0.12	0.31**	-					
5. TBR (ratio)	-0.25*	-0.11	-0.27*	-0.18	-				
6. C-RT (sec.)	-0.32**	-0.28*	-0.19	-0.14	0.35**	-			
7. C-ACC (%)	0.38**	0.38**	0.27*	0.02	-0.14	-0.15	-		
8. IC-RT (sec.)	-0.29*	-0.29*	-0.14	-0.13	0.32**	0.95**	-0.11	-	
9. IC-ACC (%)	0.29*	0.32**	0.23	0.06	-0.30**	-0.07	0.69**	-0.12	-
M	56.93	52.99	55.09	56.82	2.67	0.57	0.88	0.66	0.76
SD	26.20	26.41	29.57	26.75	0.40	0.13	0.08	0.16	0.15

**p < 0.05 and **p < 0.01. MABC-2, average percentile of the three subsets of the Movement Assessment Battery for Children-2; TBR, theta/beta ratio; C-RT, RT in the congruent condition; C-ACC, accuracy rate in the congruent condition; IC-RT, RT in the incongruent condition; IC-ACC, accuracy rate in the incongruent condition.*

TABLE 3 | Mediation Analysis for RT in the Congruent Trials of the Flanker Task (C-RT).

Variable/Effect	b	SE	t	p	95% CI	
MC→TBR	−0.0038	0.0018	−2.10	0.0391	−0.0074	−0.0002
TBR →C-RT	0.0949	0.0372	2.55	0.0130	0.0206	0.1691
MC→C-RT	−0.0012	0.0006	−2.16	0.0340	−0.0024	−0.0001
Effect						
Direct	−0.0012	0.0006	−2.16	0.0340	−0.0024	−0.0001
Indirect	−0.0004	0.0002			−0.0009	−0.0000
Total	−0.0016	0.0006	−2.77	0.0072	−0.0028	−0.0004

MC, motor competence; TBR, theta/beta ratio; CI, confidence interval.

C-ACC of the flanker task. The resting TBR played no role in the relationship between motor competence and C-ACC of the flanker task.

As shown in **Tables 5**, **6**, the motor competence could significantly predict IC-RT and IC-ACC of the flanker task and the resting TBR. Next, the resting TBR was a significant predictor of IC-RT and IC-ACC of the flanker task, respectively. While controlling for resting TBR, the result showed that the motor competence could not significantly predict IC-RT and IC-ACC of the flanker task. The results of the indirect effect indicated that the resting TBR could completely mediate a significant indirect negative relationship between motor competence and IC-RT, as well as a significant indirect positive relationship between motor competence and IC-ACC of the flanker task.

DISCUSSION

The purpose of the present study was to explore the relationships among motor competence, TBR, and inhibition function in children with ADHD. Results showed a positive association between motor competence and inhibition, whereas negative associations of TBR with motor competence and inhibition. More importantly, this study found that TBR could mediate the relationship between motor competence and inhibition. Specifically, TBR completely mediated the relationship between motor competence and response speed and accuracy in the incongruent condition of the flanker task, and partially mediated the relationship between motor competence and response speed in the congruent condition.

The results showed that motor competence was positively correlated with inhibition, which is consistent with previous findings indicating that higher motor competence is associated with better inhibition function and cognitive flexibility in children with ADHD (Hung et al., 2013; Chang et al., 2014; Pan et al., 2016). Even a single session of combined motor coordination and aerobic exercise could improve inhibition and the allocation of attentional resources in children with ADHD (Ludyga et al., 2017). Evidence from healthy individuals also indicates that motor competence is positively associated with perceived competence and multiple aspects of health including physical activity, cardiorespiratory fitness, muscular strength, muscular endurance, and a healthy weight status (Utesch et al., 2019). For example, Wu et al. (2017) showed that infants' gross motor ability assessed at 1 or 2 years old predicted cognitive inhibitory control and working memory performance 2 years later. Early developmental delay of motor competence has been found to negatively impact or coexist with additional developmental domains (e.g., cognitive, social) and/or lead to long-term health-related consequences (Brian et al., 2019). Therefore, the longitudinal impact of motor competence in early childhood should be emphasized as motor competence may influence cognitive, social, and health domains from different pathways. This is possibly due to shared neural substrates as previous research has shown that basal ganglia, the cerebellum, and the prefrontal cortex are co-activated in top-down control of behavior in both complex cognitive and motor tasks (Leisman et al., 2016).

The present study found that TBR was negatively correlated with inhibition. This finding is compatible with studies employing a Go/No-Go task (Putman et al., 2010), a flanker task (Zhang et al., 2017), and the Attentional Control Scale (Putman et al., 2014) to assess inhibition in children with ADHD or healthy individuals. Elevated theta, decreased beta, and increased TBR during the resting stage in children with ADHD may reflect a dysfunction in the frontal cortical regulation of subcortical processes (Schutter and van Honk, 2006). Compared to controls, ADHD was associated with disrupted connectivity between within-default mode network and cognitive control and affective/motivational and salience networks (Sutcubasi et al., 2020). This dysfunction may lead to inattention symptoms and inhibitory control deficits presented by a series of cognitive indicators such as increased omission errors, slower RTs, and elevated RT variability (Gambin and Święcicka, 2009). As such, a negative association between TBR and inhibition is to be expected. The present result also revealed a negative correlation between motor competence and TBR. Although no existent research identifies the influence of motor competence on TBR, Huang et al. (2018) reported that children with ADHD exhibited lower motor competence and higher TBR than typical development children. As high levels of motor competence are linked to both high working memory maintenance and effective task preparation in adolescents (Ludyga et al., 2018), the potential role of motor competence in promoting positive or negative

TABLE 4 | Mediation analysis for accuracy rate in the congruent trials of the flanker task (C-ACC).

Variable/Effect	*b*	*SE*	*t*	*p*	*95% CI*	
MC→TBR	−0.0038	0.0018	−2.10	0.0391	−0.0074	−0.0002
TBR →C-ACC	−0.0111	0.0254	−0.44	0.6631	−0.0617	0.0395
MC→C-ACC	0.0012	0.0004	3.17	0.0023	0.0005	0.0020
Effect						
Direct	0.0012	0.0004	3.17	0.0023	0.0005	0.0020
Indirect	0.0000	0.0001			−0.0001	0.0003
Total	0.0013	0.0004	3.40	0.0011	0.0005	0.0020

MC, motor competence; TBR, theta/beta ratio; CI, confidence interval.

TABLE 5 | Mediation Analysis for RT in the Incongruent Trials of the Flanker Task (IC-RT).

Variable/Effect	*b*	*SE*	*t*	*p*	*95% CI*	
MC→TBR	−0.0038	0.0018	−2.10	0.0391	−0.0074	−0.0002
TBR →IC-RT	0.1059	0.0465	2.28	0.0259	0.0131	0.1987
MC→IC-RT	−0.0014	0.0007	−1.92	0.0593	−0.0028	0.0001
Effect						
Direct	−0.0014	0.0007	−1.92	0.0593	−0.0028	0.0001
Indirect	−0.0004	0.0002			−0.0010	−0.0001
Total	−0.0018	0.0007	−2.48	0.0155	−0.0032	−0.0003

MC, motor competence; TBR, theta/beta ratio; CI, confidence interval.

TABLE 6 | Mediation Analysis for Accuracy Rate in the Incongruent Trials of the Flanker Task (IC-ACC).

Variable/Effect	*b*	*SE*	*t*	*p*	*95% CI*	
MC→TBR	−0.0038	0.0018	−2.10	0.0391	−0.0074	−0.0002
TBR →IC-ACC	−0.0918	0.0429	−2.14	0.0359	−0.1774	−0.0062
MC→IC-ACC	0.0013	0.0007	1.96	0.0530	0.0000	0.0026
Effect						
Direct	0.0013	0.0007	1.96	0.0530	0.0000	0.0026
Indirect	0.0003	0.0002			0.0000	0.0010
Total	0.0017	0.0007	2.51	0.0145	0.0003	0.0030

MC, motor competence; TBR, theta/beta ratio; CI, confidence interval.

trajectories of brain function should be noticed. Our result can be explained by the fact that high levels of motor competence is beneficial to the function of motor cortical regions such as frontal cortex and cerebellum (Halsband and Lange, 2006), which are under-aroused during the resting state in children with ADHD (Clarke et al., 2001). That is, a higher level of motor competence implies better development of these brain regions reflected by more normalized TBR.

In support of our hypothesis, inhibition, measured by response accuracy and RT at the flanker task, was predicted by motor competence, and this relationship was mediated by TBR. Previous studies indicated that ADHD-related deficits are associated primarily with the frontal-striata and frontal-parietal network (Durston et al., 2003), which are also activated during tasks requiring motor skill execution and inhibition. Therefore, high motor competence may be accompanied by improved inhibition in children with ADHD; meanwhile, biological/physiological pathways in the frontal cortex are frequently activated during the process of establishing motor competence. This positive development of neurophysiological pathways in the frontal cortex can be reflected in reduced resting TBR. Specifically, TBR was entirely responsible for the relationship between motor competence and inhibition in the incongruent condition of the flanker task, whereas TBR accounted for only part of this relationship in the congruent condition. The differences could be due to a higher demand of inhibition function in the incongruent condition. Previous studies have shown that children with ADHD make relatively more errors in the flanker task than normally developing children, especially in the incongruent condition (Crone et al., 2003). While conducting tasks exerting more complex demands on the inhibitory ability, individuals are required to make increased activation in the inferior frontal cortex, dorsolateral prefrontal cortex, and the pre-supplementary motor area to achieve the tasks (Criaud and Boulinguez, 2013). On the other hand, task performance in the congruent condition may be affected by brain regions other than the frontal cortex due to there being less demand on executive function. For individuals who have higher motor competence, they may exhibit fewer inattentive symptoms reflected by reduced resting TBR. Therefore, in more complex tasks, they are more likely to mobilize relevant cognitive resources to meet the high levels of cognitive demand. The mediating role of TBR in the relationship between motor competence and inhibition in children with ADHD is becoming increasingly apparent under this situation. These ideas are speculative and future work is required before any definitive conclusions can be drawn.

Caution should be exercised when interpreting the results of this study. First, although the results found possible relationships among motor competence, resting TBR, and inhibition, experimental studies are needed to provide stronger evidence for the causal nature of this relationship. Second, the number of correct trials in the incongruent condition would be too small to calculate RT appropriately. Although the current study followed the research protocol used in Tsai et al. (2017), a smaller number of trials and higher error rate in the incongruent condition may result in inaccurate estimate of RT. Third, given that increased TBR and weaker inhibition function in ADHD populations compared with healthy control groups have been identified, this study did not utilize a sample of normally developing children as a control group. The inclusion of such a group would enable a determination of the extent to which the mediating effect of TBR in the relationship between motor competence and inhibition is specific to children with ADHD, or if it reflects a general relationship between motor competence and inhibition regardless of whether ADHD is present. In summary, the current study found that inhibition is predicted by motor competence, and this relationship is mediated by TBR in children with ADHD. This finding has significant implication in the interpretation of the relationship between motor competence and inhibition function in children with ADHD. Also, given that inhibition is thought to play an important role in mood regulation, social relationships, academic learning and future development in children with ADHD, participation in physical exercise aiming at improving both motor abilities and physical fitness may have greater implications for their development. For future researchers, our findings suggest that other mediators could exist and need to be further explored. It is also recommended that future studies look at the relationship of different facets of motor competence to subcomponents of executive functions in order to describe this relationship in more detail.

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 Institutional Review Board of National Taiwan Normal University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

C-FL and C-JH were responsible for the research idea, implementing the study, and manuscript writing up. C-LH was responsible for the statistical support and discussion commentary. Y-JT and T-YC were responsible for assisting on the data collection and analysis. Y-KC was responsible for consulting the methodology and interpretation of the findings. T-MH was responsible for the discussion of the research idea, supervision of the data collection, and comment on the manuscript writing up. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Can Exercise Reduce the Autonomic Dysfunction of Patients With Cancer and Its Survivors? A Systematic Review and Meta-Analysis

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Background: Cancer therapies have increased patient survival rates, but side effects such as cardiotoxicity and neurotoxicity can lead to autonomic nervous and cardiovascular system dysfunction. This would result in a decrease in parasympathetic activity and the enhancement of sympathetic activity. Heart rate variability (HRV), which reflects autonomic modulation, is a valuable physiological tool since it correlates with cancer-related fatigue, stress, depression, and mortality in patients with cancer.

Objective: This study aimed to analyze the effects of exercise programs on the autonomic modulation, measured by the HRV of patients with cancer and its survivors.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed, and the quality of the articles was assessed with the Physiotherapy Evidence Database (PEDro) scale. The meta-analysis statistic procedure was performed by using RevMan software version 5.3.

Results: From the 252 articles found, six studies were included in the review involving 272 participants aged 30–75 years. Exercise programs had a mean length of 10.4 $\pm$ 4.6 weeks, a frequency of 3 $\pm$ 1.4 days/week, and a mean duration of 78 $\pm$ 23.9 min. In time-domain HRV measures, exercise may increase in the SD of normal-to-normal intervals [$p < 0.00001$, with a mean difference (MD) of 12.79 ms from 9.03 to 16.55] and a decreased root mean square of successive R–R interval differences ($p = 0.002$, with an MD of 13.08 ms from 4.90 to 21.27) in comparison with control groups (CG). The frequency-domain data reveal that the exercise group (EG) improve significantly more than the CGs in low frequency [absolute power: $p < 0.0001$, with a standardized mean difference (SMD) of 0.97 from 0.61 to 1.34; relative power: $p = 0.04$, with an MD $= -7.70$ from -15.4 to -0.36], high-frequency [absolute power: $p = 0.001$, with a SMD of 1.49 from 0.32 to 2.66; relative power: $p = 0.04$, with an MD of 8.00 normalized units (n.u.) from 0.20 to 15.80], and low-to-high frequency ratio ($p = 0.007$ with an MD of -0.32 from -0.55 to -0.09).

Conclusion: Exercise programs could lead to positive effects on the autonomic modulation of patients with cancer and its survivors. More beneficial changes may occur with resistance and endurance workouts. However, due to the low number of interventions performed, further research is needed to substantiate the findings and to provide additional insights regarding the exercise intensity required to increase the autonomic modulation of the patient.

Keywords: autonomic modulation, exercise programs, cardiovascular dysfunction, oncology, heart rate variability

INTRODUCTION

Modern advances in cancer therapy have resulted in increased survival rates. However, patients are frequently affected by various negative side effects (Miller et al., 2019). In particular, both the autonomic control impairment and the increased risk of cardiovascular disease (Lakoski et al., 2015) are suffered by ∼80% (Coumbe and Groarke, 2018) and 42% (Chen et al., 2012) of the patients, respectively. The autonomic nervous system (ANS) is the main homeostatic regulatory system of the body, involved in the etiology and the clinical course of cancer therapies (Simó et al., 2018). Chemotherapy and radiotherapy cause cardiotoxicity (Scott et al., 2014) and neurotoxicity (Park et al., 2013), thereby affecting ANS and cardiovascular function. The cardiovascular ANS needs to be controlled during the cancer phases to regulate levels of autonomic dysfunction of patients (Walsh and Nelson, 2002).

Heart rate variability (HRV) is a noninvasive tool to evaluate the autonomic modulation of the sinus node in healthy, cardiac, and noncardiac disease populations (Lombardi and Stein, 2011). In patients with cancer, HRV is a useful, effective, and more practical method to assess autonomic dysfunction than other validated methods, which are more complex to apply (Guo et al., 2013). HRV measures provide a multidimensional register of autonomic modulation, including the sympathetic and parasympathetic modulation of cardiac function (Arab et al., 2016), which is notably modified in patients with cancer compared with the healthy population. Studies including wide sample sizes have found significantly lower values in the root mean square of successive R–R interval measures (RMSSD), representing the parasympathetic activity, and the SD of the interbeat interval of normal sinus beats (SDNN) (i.e., overall HRV measure) of patients with cancer compared with the healthy population (De Couck and Gidron, 2013; Bijoor et al., 2016). Cancer-treating drug therapies induce cardiac abnormalities, such as heart failure, myocardial ischemia, myocarditis, hypertension, or arrhythmias, among others (Chang et al., 2017), detected with HRV even with normal systolic left ventricular function (Tjeerdsma et al., 1999) with an overactivation of the sympathetic nervous system (SNS) and a decrease in the parasympathetic nervous system (PNS) activity (Coumbe and Groarke, 2018). Consequently, this imbalance, produced by cancer drugs, may stimulate the hypothalamic-pituitary-adrenal axis and the endocannabinoid and renin-angiotensin-aldosterone systems producing an increase in oxidative stress, chronic inflammation, and atherosclerosis with a reduction in vasodilation, which affects the health of patients (Lakoski et al., 2015). Several types of research have focused on the relationship between the global HRV modifications and the health of patients with cancer obtaining an inverse correlation with cancer-related fatigue (Fagundes et al., 2011) and depression (Giese-Davis et al., 2006). Findings also show the role of HRV to predict survivorship being higher when the vagal nerve activation is stimulated (Zhou et al., 2016).

Palma et al. (2020) and Dias Reis et al. (2017) published a systematic review of supportive therapy modalities that have been developed to reduce the HRV results. They found interventions based on music therapy, traditional Chinese medicine-related treatments, exercise, relaxation, and myofascial release techniques and concluded that HRV seemed to be a safe and easily applicable method to assess cancer-related autonomic dysfunction (Palma et al., 2020). However, not only the consequences of cancer therapy need to be considered to improve HRV but also the lifestyles of patients can influence it negatively (Scott et al., 2014). Thus, a multifactorial intervention that could modify the physiological changes mentioned earlier and other health and psychological parameters is crucial to globally benefit the patients with cancer.

Exercise programs appear to promote physiological changes leading to reduce the decline of the autonomic modulation and improving its levels during (Mostarda et al., 2017) and after cancer treatments (Shin et al., 2016). Scott et al. (2014) approximated the benefits of aerobic exercise training to the autonomic modulation of patients with cancer stating that it may decrease sympathetic tone and increase vagal tone by the influence of exercise in attenuate cardiovascular abnormalities as heart failure or coronary artery disease. Aerobic exercise modifies the renin-angiotensin-aldosterone system (Scott et al., 2014) and stimulates the hypothalamic-pituitary-adrenal axis suppressing angiotensin II expression, which promotes the sympathetic activity of the ANS (Routledge et al., 2010). Consequently, the stimulation of the hypothalamic-pituitary-adrenal axis and the endocannabinoid and renin-angiotensin-aldosterone systems is produced (Arab et al., 2016). Exercise also upregulates nitric oxide promoting vasodilation (Kingwell, 2000; Scott et al., 2014) reduces reactive oxygen species induced by chemotherapy toxicity (Scott et al., 2014). Moreover, regarding the remaining physiological changes mentioned earlier, exercise can also decrease chronic inflammation (Gleeson et al., 2011), improving the immune system and the stimulation of natural killer cells (Khosravi et al., 2019). Exercise can also reduce body mass index (BMI) (Thomas et al., 2017), which may be correlated to an HRV increase (Arab et al., 2016). Although exercise may have the potential role to increase HRV, the results presented by the different interventions developed are controversial considering all the variables inside HRV. In this way, this systematic review and meta-analysis aimed to evaluate the effects of exercise interventions on the autonomic function of patients with cancer and its survivors analyzing the measures involved.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines have been followed to develop the systematic review (Liberati et al., 2009). Before the data extraction was performed, the study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) by the following identification number: CRD42020191041.

Search Strategy

The databases employed for searching the articles were Web of Science (including studies indexed in the KCI-Korean Journal Database, MEDLINE, Russian Science Citation Index, SciELO Citation Index, and PubMed (MEDLINE). The terms used for the search were as follows: cancer and neoplasms, separated by OR; and HRV, autonomous nervous function, autonomous nervous system, separated by OR; and exercise, training, physical activity, also separated by OR. The only filter employed was the requirement of being articles written in English or Spanish. The search was carried out from April 2020 to June 2020.

The articles found were included if they fulfilled the following criteria: (1) the target population was patients with cancer or survivors, (2) the program involves any physical exercise, (3) the investigation assesses and reports any HRV variable, (4) the study includes at least one control group (CG) whose results are compared with an exercise group (EG). Moreover, the following exclusion criteria were set: (1) the article was a review, letter to the editor, conference abstract, case report, or study protocol, (2) the study did not evaluate the HRV variables directly after the intervention, and (3) the studies were completely written in a language different from English or Spanish.

Risk of Bias Assessment

The analysis of the risk of bias was performed using the Physiotherapy Evidence Database (PEDro) scale, known as a valid and reliable instrument to assess eligibility, allocation to groups, blinding of allocation, and comparison between groups at baseline and its outcomes (Maher et al., 2003). The leading reasons for its selection were due to it being the most used in the scientific area of the Sport Sciences for Health and it is a specific tool focused on physical therapies (Moseley et al., 2020).

Data Extraction

Participants, Interventions, Comparisons, and Study Designs Information

The main information of the articles is reported in the tables and figures in the article and the supplementary data. Regarding participants, CG and EG baseline parameters were extracted, such as sample size, mean age, BMI, physical activity level, cancer type, stage, type of treatment, and timing. The intervention characteristics included the length of the program, duration of each session, weekly frequency, exercise description, intensity, progression, and adherence. The intervention of the comparison group was also extracted.

HRV Outcome Measurements

Interventions included an HRV assessment before and after the intervention. For consistency in measures, participants were laid in a supine position (Niederer et al., 2013; Dias Reis et al., 2017; Zhou et al., 2018) or seated in chairs (Shin et al., 2016; Lee et al., 2018). HRV was recorded for 5 min of adequate stationary sign (Niederer et al., 2013; Lee et al., 2018; Zhou et al., 2018) with Polar S810© (Niederer et al., 2013), CANS 3000 (Laxtha, Daejeon, Korea) (Shin et al., 2016), or CheckMyHeart Handheld HRV (Lee et al., 2018) by using ECG (Zhou et al., 2018). The spectral analysis from the artifact-free data was performed by the fast Fourier transformation with the Kubios HRV Analysis software (Niederer et al., 2013; Dias Reis et al., 2017; Mostarda et al., 2017; Zhou et al., 2018) or AcqKnowledge (Zhou et al., 2018). The results of this review include two HRV variables in the time domain, namely, SDNN and RMSSD. In the frequency domain, the low-frequency (LF) band, the high-frequency (HF) band, the ratio of LF-to-HF (LF/HF), and the total power (TP), calculated as the sum of the energy in very-low-frequency (VLF), LF, and HF bands, were extracted (Shaffer and Ginsberg, 2017). The frequency-domain data were reported in absolute units by using milliseconds squared (ms^2) or normalized units (n.u.) obtained by diving the result between the TP and multiplied to 100 [i.e., LF or HF/(TP–VLF) × 100] (Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996). SDNN and RMSSD were measured in 1/1,000 s (milliseconds) (Shin et al., 2016), and HF was recorded from 0.15 to 0.4 Hz and LF from 0.04 to 0.15 Hz (**Table 3**) (Niederer et al., 2013; Shin et al., 2016; Dias Reis et al., 2017; Mostarda et al., 2017; Zhou et al., 2018).

Statistical Analysis

The analysis was performed with the post-intervention means and SDs of the EG and the CG collected from the articles. The meta-analysis statistical tool used was the Review Manager Software (RevMan software version 5.3) (RevMan, 2014). The selected method was the inverse variance with random effects and a 95% CI (Schmidt et al., 2009). Additionally, the I^2 model was used to calculate the heterogeneity of the results. The results were presented with a standardized mean difference (SMD) when the same variable was measured in different units (i.e., ms^2 and log ms^2) as occurred with the absolute power variables of HF and LF. In contrast, the mean difference (MD) was used when all studies assessed the variable using the same units (n.u. or ms). According to the *Cochrane Handbook for Systematic Reviews of Intervention*, the SMD effects were interpreted as small with results <0.4, moderate from 0.4 to 0.7, and large >0.7 (Higgins and Green, 2011).

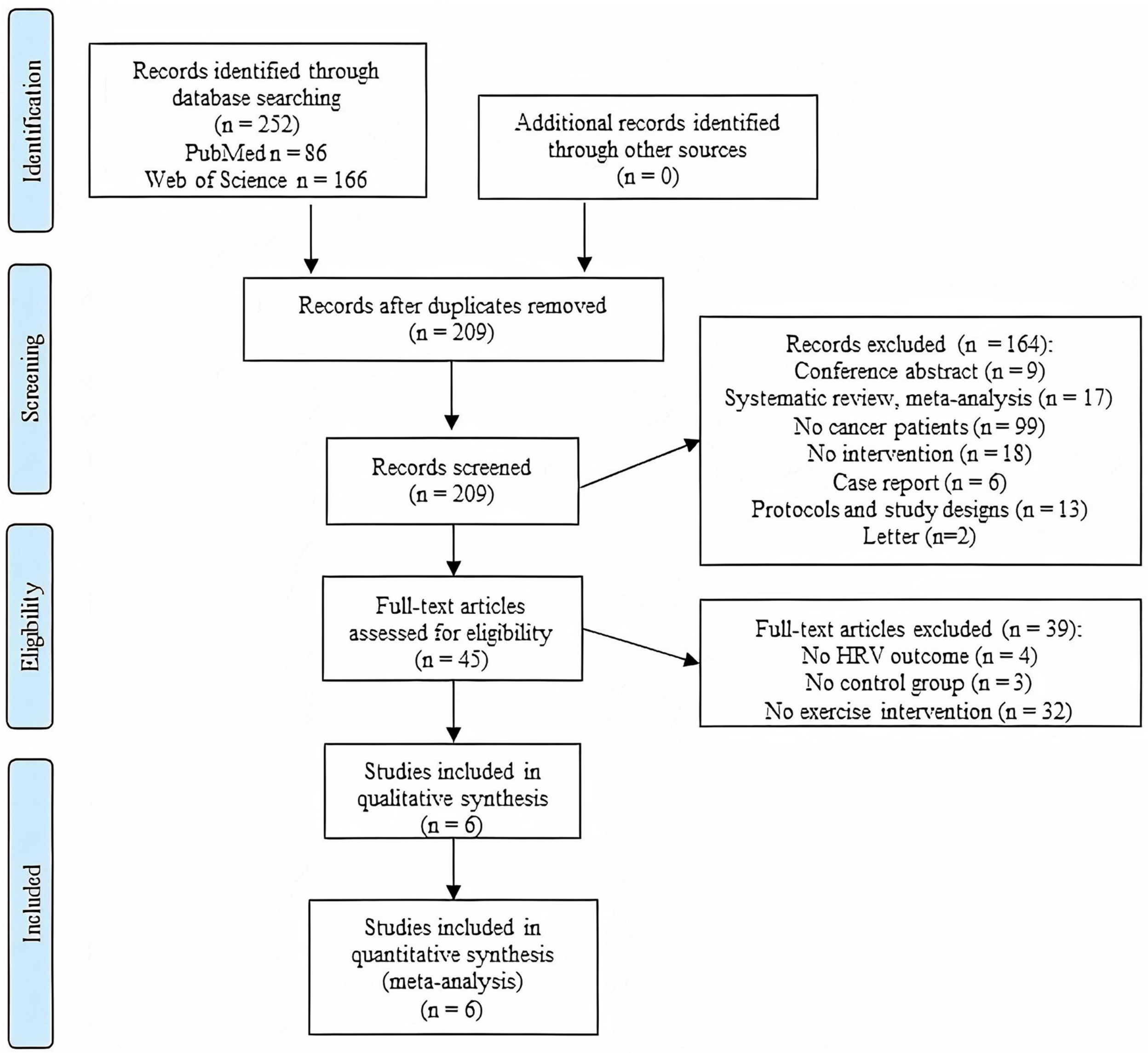

FIGURE 1 | Study flow diagram following the preferred reporting items for systematic reviews and meta-analyses guidelines.

RESULTS

Study Selection

About 252 articles were identified in Web of Science ($n = 166$) and PubMed ($n = 86$) scientific databases. **Figure 1** shows the flow diagram where 209 articles were analyzed after removing the duplicates. Two hundred and three articles were excluded after reading the title or the abstract ($n = 164$) or after the full-text evaluation ($n = 39$). Therefore, both the systematic review and the meta-analysis were developed with six studies published between 2012 and 2018.

Risk of Bias

In the PEDro scale, as **Table 1** shows the mean score obtained was 5, and the external validity was 5, ranging from 4–7 (10 being the highest possible mark). The five articles assessed positively reached the external validity (item 1) and the statistic items (items 10 and 11). However, the internal validity punctuation was more heterogeneous. None of the evaluated studies met items 5, 6, and 7 related to the blinding process, difficult to fulfill in sport sciences.

Participants Characteristics

The baseline information of the participants is reported in **Table 2**. The total sample size of the systematic review was 272, out of which 126 were included in the CG and 146 in the EG, and the sample was mainly composed of women. The ages ranged from 30 to 75 years, although most of the participants were older than 45 years of age. Different types of cancer were included in this study as follows: three interventions contained only patients with breast cancer (Shin et al., 2016; Dias Reis et al., 2017;

TABLE 1 | Risk of bias using the PEDro scale.

Validity	External item	Internal items								Statistic items		TOTAL score
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Lee et al. (2018)	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5
Zhou et al. (2018)	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	6
Dias Reis et al. (2017)	Yes	No	No	Yes	No	No	No	Yes	No	Yes	Yes	4
Mostarda et al. (2017)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7
Shin et al. (2016)	Yes	No	No	Yes	No	No	No	Yes	No	Yes	Yes	4
Niederer et al. (2013)	Yes	No	No	Yes	No	No	No	Yes	No	Yes	Yes	4

Items: 1, eligibility criteria were specified; 2, subjects were randomly allocated to groups; 3, allocation was concealed; 4, the groups were similar at baseline; 5, there was blinding of all subjects; 6, there was blinding of all therapists; 7, there was blinding of all assessors; 8, measures of at least one key outcome were obtained from more than 85% of the subjects who were initially allocated to groups; 9, the intention-to-treat analysis was performed on all subjects who received the treatment; 10, the results of the between-group statistical comparisons are reported for at least one key outcome; 11, the study provides both point measures and measures of variability for at least one key outcome; total score, each satisfied item (except the first) contributes 1 point to the total score, yielding a PEDro scale score that can range from 0 to 10.

Mostarda et al., 2017) and two incorporated various types of cancer such as colorectal, lung, breast, genital, gastrointestinal, and hematological (Niederer et al., 2013; Lee et al., 2018). One study contained only nasopharyngeal cancer (Zhou et al., 2018). The patients participated in the exercise program during the treatment of cancer drugs (i.e., chemotherapy, radiotherapy, and hormonotherapy) (Niederer et al., 2013; Shin et al., 2016; Zhou et al., 2018) or after finishing the treatments (Niederer et al., 2013; Dias Reis et al., 2017; Mostarda et al., 2017; Lee et al., 2018).

Intervention Characteristics

The exercise interventions included in this review are detailed in **Table 3**. The length of the exercise program varied from 4 weeks (Mostarda et al., 2017) to 16 weeks (Niederer et al., 2013), with one intervention conducted during the entire chemotherapy cycle of 19 months (Zhou et al., 2018). Participants attended exercise sessions once per week (Lee et al., 2018), three times per week (Shin et al., 2016; Dias Reis et al., 2017; Mostarda et al., 2017), and five times per week (Zhou et al., 2018), whereas Niederer et al. (2013) suggested patients exercise 3–5 times per week. Together with the study of Zhou et al. (2018), their interventions were the only programs that included an unsupervised exercise element. Sessions lasted from 60 to 120 min (Niederer et al., 2013; Lee et al., 2018; Zhou et al., 2018), with a median of a 70-min exercise (Shin et al., 2016; Dias Reis et al., 2017; Mostarda et al., 2017).

Two exercise programs were based on oriental exercise techniques, such as Tai Chi (Zhou et al., 2018) and Qigong (Lee et al., 2018), including a meditation component. The remaining interventions involved cardiovascular and resistance training (Niederer et al., 2013; Shin et al., 2016; Dias Reis et al., 2017; Mostarda et al., 2017), including the program conducted by Niederer et al. (2013), where patients were counseled to exercise following the recommendations of the ACSM Roundtable on Exercise Guidelines for Cancer Survivors (Schmitz et al., 2010) and could participate in guided Nordic Walking sessions once per week. Dias Reis et al. (2017) and Mostarda et al. (2017) incorporated the cardiovascular cycling of 30 min and different free weight exercises, such as squats, shoulder press, hip flexion, or French press, among others (Dias Reis et al., 2017; Mostarda et al., 2017). In contrast, Shin et al. (2016) used circuit training to develop the sessions combining strength and cardiovascular exercises and using the rate of perceived exertion (RPE) to monitor and progress the intensity (Shin et al., 2016).

HRV Results

Most of the studies reported the outcome results after treatment. However, one study (Lee et al., 2018) only reported the change from baseline. Therefore, it was excluded from this meta-analysis. Other than the study of Niederer et al. (2013), the outcomes of the EG after cancer treatment were extracted (Niederer et al., 2013). The results were then divided into time and frequency domains to present how exercise influences patients with cancer and survivors in these domains.

Regarding the HRV time-domain measure analysis, in SDNN EG, there were significant increases compared with the CG with a $p < 0.00001$ (MD of 12.79 and a 95% CI from 9.03 to 16.55) (**Figure 2**). Also, Lee et al. (2018) found significant differences between groups analyzing the change from baseline ($p = 0.001$) (Lee et al., 2018). Participants in the EG also reached higher increases on RMSSD compared to those in the CG ($p = 0.002$ with an MD of 13.08 ms and 95% CI from 4.90 to −21.27) (**Figure 3**).

As for the frequency-domain outcomes, the LF and HF results were obtained in SMD from the analysis of the absolute power (ms^2 or log ms^2), and that in MD, the relative power (n.u.). **Figure 4** shows that LF was significantly increased in the EG compared to the CG in both analyses. In absolute power, results had a p-value of <0.0001 and an SMD of 0.97 with a 95% CI from 0.61 to 1.34, while in n.u., the p-value was 0.04 with an MD of −7.70 n.u. and a 95% CI from −15.04 to −0.36. The HF results, which are presented in **Figure 5**, of the EG in absolute

TABLE 2 | Baseline characteristics of participants.

Study	Design	Group	*N* (% females)	Age	Cancer type	Cancer stage	Cancer treatment (type or timing)
Lee et al. (2018)	RCT	CG	26 (84.6%)	30–39 (3.8%), 40–49 (19.2%), 50–59 (57.7%), 60–69 (11.5%), and 70–75 (7.7%)	Colorectal (11.5%), lung (3.8%), breast (69.2%), gynecological (7.7%), and other (7.7%)	I (42.3%), II (26.9%), III (26.9%), and none (3.8%)	After treatment: surgery, chemotherapy, radiotherapy, and target therapy
		EG	29 (86.2%)	30–39 (10.3%), 40–49 (24.1%), 50–59 (37.9%), 60–69 (17.2%), and 70–75 (10.3%)	Colorectal (6.9%), lung (3.4%), malignant lymphoma (3.4%), breast (62.1%), gynecological (6.9%), and other (17.2%)	I (24.1%), II (51.7%), III (20.7%), and none (3.4%)	
Zhou et al. (2018)	RCT	CG	57 (21.05%)	<30 (12.3%), 30–50 (64.9%), and >50 (22.8%)	Nasopharyngeal	III (40.3%), IV a/b (59.6%)	During treatment: chemotherapy and radiotherapy
		EG	57 (33.33%)	<30 (22.8%), 30–50 (59.6%), and >50 (17.5%)		III (35.1%), IV a/b (64.9%)	
Dias Reis et al. (2017)	Controlled trial	CG	9 (100%)	45 ± 7	Breast	I, II, and III	After treatment: hormonal therapy, chemotherapy, and radiotherapy
		EG	9 (100%)	48 ± 7.2			
Mostarda et al. (2017)	RCT	CG	9 (100%)	Range 30–59	Breast	I, II, and III	After treatment: hormonal therapy (33.3%), chemotherapy (27.8%), and radiotherapy (38.9%)
		EG	9 (100%)				
Shin et al. (2016)	Controlled trial	CG	10 (100%)	49.2 (range, 35–60)	Breast	0 (10%), I (20%), II (60%), and III (10%)	During treatment: anticancer treatment (80%) and radiotherapy (30%)
		EG	12 (100%)	46.3 (range, 35–66)	Breast	0 (8.3%), I (33.3%), II (50%), and III (8.3%)	During treatment: anticancer treatment (83.3%), radiotherapy (91.7%)
Niederer et al. (2013)	Controlled trial	CG	15 (60%)	61.6 ± 10.6	Each group: Gastrointestinal (20%), genital and breast (26.67%), diagnosis bronchial (13.33%), hematological (6.67%), and other (33.33%)	0, I, and II	Chemotherapy 12, Radiotherapy1, and Hormone therapy2
		EG (during)	15 (60%)	59.6 ± 9.4		0, I, and II	During treatment: Chemotherapy 14 and Radiotherapy1
		EG (after)	15 (60%)	60.7 ± 6.7		0, I, and II	After treatment

RCT, randomized controlled trial; CG, control group; EG, exercise group.

power measures, were significantly higher than the CG outcomes ($p = 0.001$, and an SMD of 1.49 with a 95% CI from 0.32 to 2.66) and their effects on the relative power units ($p = 0.04$, and an MD of 8.00 n.u. with a 95% CI from 0.20 to 15.80). Moreover, Lee et al. (2018) stated that significant differences in the change from baseline reveal but not between groups (Lee et al., 2018). The ratio LF/HF showed significant differences between EG and CG with a p-value of 0.007 and an MD of −0.32 (95% CI from −0.55 to −0.09), as represented in **Figure 6**. Finally, the TP data was not analyzed by meta-analysis only two studies include the measure (Niederer et al., 2013; Lee et al., 2018). Niederer et al. (2013) stated the significant differences in the interaction between groups (i.e., exercise during treatment group, exercise after treatment group, and CG) and time (before and after intervention) with a p-value of 0.025. However, their *post-hoc* analysis showed high differences between after treatment group and the CG ($p = 0.012$). As for the results of Lee et al. (2018), the Qigong EG significantly increases TP with a p-value of 0.002 from baseline to after intervention.

DISCUSSION

This systematic review and meta-analysis aimed to evaluate the effects of exercise interventions in the HRV of cancer patients and survivors. The data obtained showed significant differences between the EG and the CG in all the variables analyzed as follows: SDNN, RMSSD, LF (ms^2 and n.u.), HF (ms^2 and n.u.), LF/HF ratio, and TP. Thus, exercise interventions may improve the autonomic control in patients with cancer and reduce the risk of autonomic dysfunction of participants. However, some specifications need to be considered due to the heterogeneity

TABLE 3 | Characteristics of exercise interventions and heart rate variability (HRV) measurements.

Study	Group	Length	Sessions duration	Weekly frequency	Exercise description	HRV measurement and analyses process
Lee et al. (2018)	CG	12 weeks				Tool: CheckMyHeart Handel HRV ECG Duration: 5 min Position: seated or lying prone HRV variables: SDNN, TP, and HF Analysis information
	EG	12 weeks	120 min	1 time/week	Qigong: standing position, meditation, and leg massage.	
Zhou et al. (2018)	CG	During the chemotherapy of 19 months				Tool: ECG Duration:5 min Position: supine HRV variables: LF, HF, and LF/HF Analysis information: AcqKnowledge and Kubios and relative power and normalized units computation for frequency variables
	EG		60 min	5 times/week	Supervised or instructional video Tai Chi exercise: Warm up: 10 min Main part: 30 min Tai Chi exercise and 10 min of breathing and meditation Relaxation: 10 min	
Dias Reis et al. (2017)	CG	12 weeks				Tool: Tachogram Duration: 5 min Position: supine HRV variables: SDNN, RMSSD, LF, HF, and LF/HF Analysis information: beat-to-beat interval of iR–R, manually and automatic Kubios software filter, beat-by-beat sets were converted to equidistant time series and then applied the FFT
	EG	12 weeks	≈70 min	3 times/week	Cardiovascular training: 30 min cycle ergometer (60% VO_{2max}) Resistance training: free weight exercise (hip flexion and extension, shoulder press, free squad, French triceps press, curved row General stretching: maintained each exercise 20–30 s	
Mostarda et al. (2017)	CG	4 weeks				Tool: Tachogram Duration: 5 min Position: NR HRV variables: SDNN, RMSSD LF, HF, LF/HF Analysis information: beat-to-beat interval of iR-R, manually and automatic Kubios software filter, FFT, and normalized units computation
	EG	4 weeks	70 min	3 times/week	Cardiovascular training: 30 min cycle ergometer (60% VO_{2max}) Resistance training: squat, shoulder press, hip flexion, barbell bent over row, and French press	
Shin et al. (2016)	CG	8 weeks				Tool: CANS 3000 (wrists and ankles and electrodes) Duration: 5 min Position: sitting HRV variables: SDNN, RMSSD, LF, HF, LF/HF Analysis information: R–R interval (1/1,000 s)
	EG	8 weeks	70 min	3 times/week	Warm up: 10 min gymnastics and stretching (upper body) Main exercises: 40 min circuit exercises (Shaking while running in place, flank, running in place, squat, walking in place, crunch, step, lunge, running with open arms, back muscle exercise) Intensity control: RPE. Progression from 9 to 14 RPE Cool down: 15 min gymnastics and stretching	
Niederer et al. (2013)	CG	16 weeks				Tool: Polar S810 Duration: 5 min Position: supine HRV variables: TP, HF, LF Analysis information: FFT, Kubios HRV Analysis, Biosignal Analysis, and logarithmic values.
	EG (during)	16 weeks	NR (only recommen dations)	NR (only recommen dations)	Home-based training counseling (recommendation 3–5 times per week, 1 h, at 70–90% of individual anaerobic threshold, 13–14 RPE) and the opportunity to participate in a guided Nordic-Walking training (1 time/week)	
	EG (after)	16 weeks				

CG, control group; EG, exercise group; NR, not reported; VO_{2max}, maximum oxygen consumption; RPE, the rating of perceived exertion; SDNN, SD of the interbeat interval of normal sinus beats; RMSSD, root mean square of successive differences between normal heartbeats; LF, low-frequency band; HF, high-frequency band; LF/HF, Ratio of LF-to-HF; TP, Total Power; FFT, fast Fourier transform.

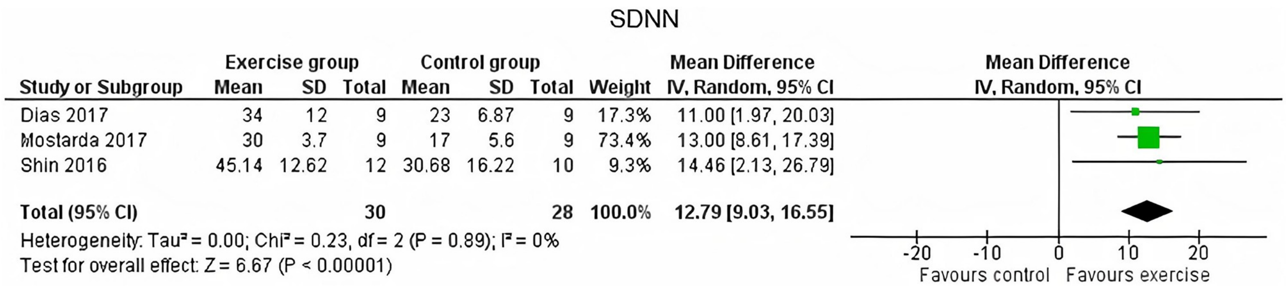

FIGURE 2 | Effects of exercise in SDNN (standard deviation of the interbeat interval of normal sinus beats) heart rate variability measure.

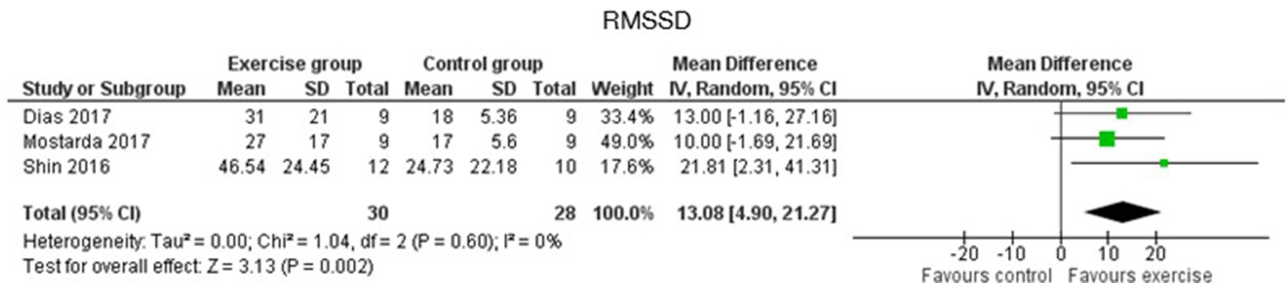

FIGURE 3 | Effects of exercise in RMSSD (root mean square of successive differences between normal heartbeats) heart rate variability measure.

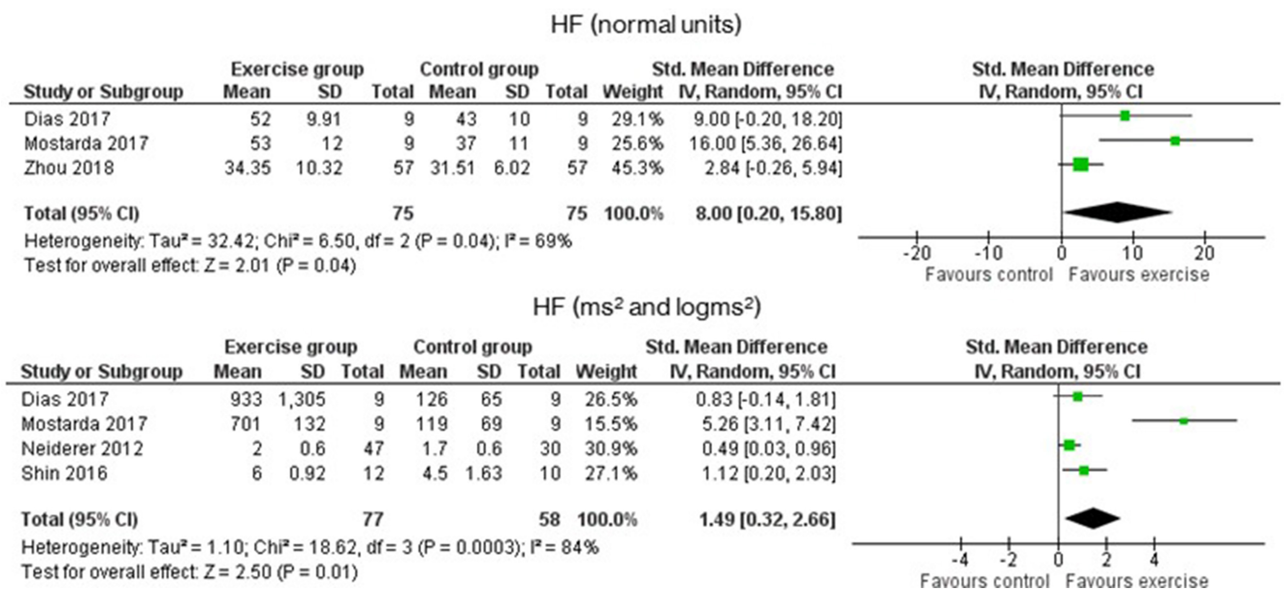

FIGURE 4 | Effects of exercise in HF (High Frequency) heart rate variability measure expressed in absolute (ms^2) and relative (n.u) power.

of the programs and the physiological implications of the variables analyzed.

Although we have included all the variables measured in the HRV, the physiological interpretation of some of these variables of ANS recording is controversial. Only RMSSD and HF have been proven to reflect the PNS activity to date (Shaffer and Ginsberg, 2017), whereas the reflection of SNS or PNS in SDNN, LF, and LF/HF is not clear. SDNN seems to measure the overall HRV with the contribution of sympathetic and parasympathetic modulation, but in the short-term resting recordings, the main source of the variation could be provided from the SNP (Shaffer and Ginsberg, 2017). The LF physiological interpretation is still

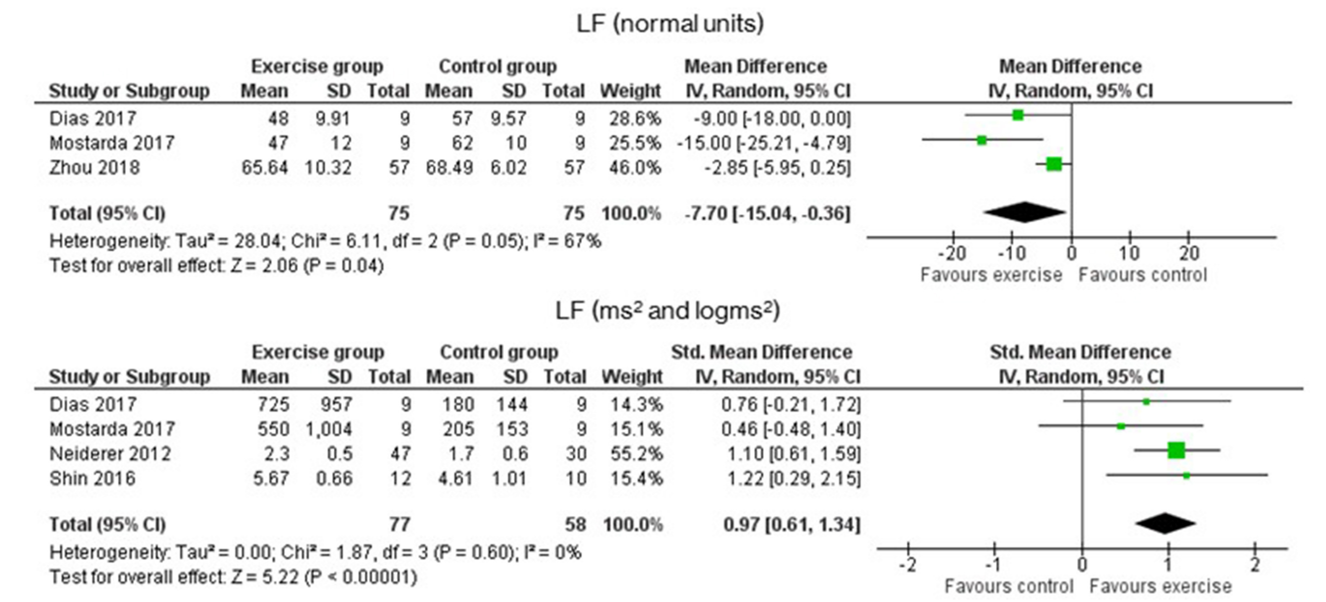

FIGURE 5 | Effects of exercise in LF (Low Frequency) heart rate variability measure expressed in absolute (ms^2) and relative (n.u) power.

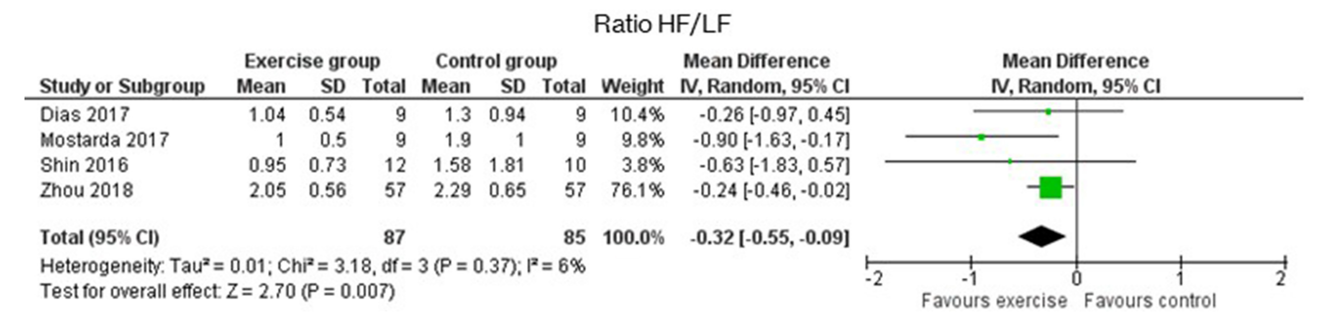

FIGURE 6 | Effects of exercise in Ratio HF/LF (ratio of Low Frequency to High Frequency) heart rate variability measure.

not universally agreed since some researchers assume it as an index of cardiac sympathetic control (Reyes Del Paso et al., 2013), whereas more current literature state that it may principally reflect the baroreflex activity (Goldstein et al., 2011) or even being mainly determined by the PSN (Reyes Del Paso et al., 2013). However, it seems to depend on the band recording frequency having a possible SNS implication if it reaches 0.1 Hz (Shaffer and Ginsberg, 2017). Consequently, the physiological interpretation of the LF/HF ratio is also uncertain due to LF not being a pure SNS index (Goldstein et al., 2011; Shaffer and Ginsberg, 2017). With this in mind, the following discussion will be focused on the HF and RMSSD physiological values to argue the overall autonomic control effects.

In line with HRV parasympathetic activity variables of the CGs, several articles have revealed the effects of cancer treatments in RMSSD and HF and the overall measure of SDNN. Surgery, for instance, significantly reduces RMSSD and SDNN even 14 days post-op (Hansen et al., 2013), which is similar to what occurs after administration of a high dose of chemotherapy and its subsequent cardiotoxicity (Kloter et al., 2018). This ANS dysfunction reduces the release of catecholamine neurotransmitters, which could negatively influence the regulation of the tumor microenvironment (Hanns et al., 2019). Cancer decreases catecholamine production, with a concomitant rise in oxidative stress, inflammation, and cancer progression (Cole et al., 2015). Under normal conditions, the PNS could regulate the inflammatory response, but the decline of the vagal nerve activity produced by cancer may inhibit inflammatory regulation (Williams et al., 2019). In this way, in contrast to healthy controls with similar characteristics, patients with breast cancer have significantly lower RMSSD, HF, and SDNN values 1 year after treatment (Caro-Morán et al., 2016). Consequently, when comparing the HRV results with the normal values of healthy individuals, the differences are notable (Nunan et al., 2010). Thus, the role of PNS and its variance is so crucial in cancer prognosis that having a high HF power is positively

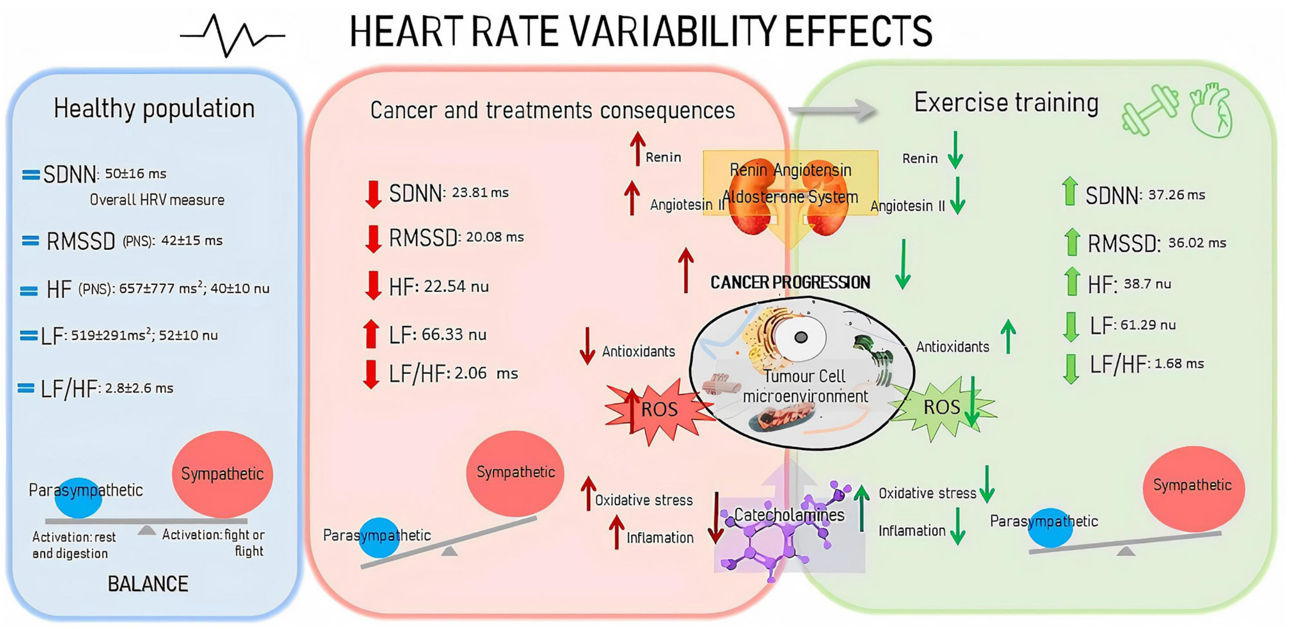

FIGURE 7 | Explication of the changes in the heart rate variability of cancer patients and exercise training effects in comparation to healthy population data. Healthy population of HRV data from Nunan et al. (2010), cancer and treatments consequences and exercise effects data correspond to control and exercise group after intervention results of the current systematic review. References from the physiological changes in cancer patients and its exercise effects are reported in the systematic review discussion. SDNN, standard deviation of the interbeat interval of normal sinus beats; RMSSD, root mean square of successive RR interval measures; HF, high frequency; LF, low frequency; LF/HF, low-to-high frequency ratio; PNS, parasympathetic nervous system; ROS, reactive oxygen species.

correlated with survival in patients with advanced breast cancer (Giese-Davis et al., 2015).

Exercise seems to have a positive influence on the ANS of patients with cancer and its related physiological consequences, as shown in **Figure 7**, illustrates, in this case, the recovery to the normal values of HRV measures after the interventions. Exercise can induce the increase of catecholamines, which are commonly reduced due to cancer and lead to positive changes in tumor hypoxia, angiogenesis, metabolic stress, and cell immunity (Hojman et al., 2018) by the lactate production, according to the Warburg effect (San-Millán and Brooks, 2016). This would increase the parasympathetic responses and decrease the local oxidative stress and DNA damage, i.e., inflammatory reactions (De Couck et al., 2012). Consequently, the ability of cancer cells to form tumors in distinct tissues (Hojman et al., 2018) and the risk of developing metabolic abnormalities (Licht et al., 2010) related to poor cancer prognosis (De Couck et al., 2012) could be reduced. Moreover, exercise may also benefit patients by increasing the vagal nerve stimulation in the renin-angiotensin-aldosterone system (Miller and Arnold, 2019). When this occurs, there may be a reduction in the renin enzyme production (Cunha et al., 2016), with subsequent angiotensin II reduction, thereby affecting the cholinergic parasympathetic neurotransmission to the heart (Miller and Arnold, 2019). These mechanisms control angiogenesis, tumorigenesis, metastasis, and cellular proliferation (Munro et al., 2017). Few articles relate the effects of exercise in the renin-angiotensin-aldosterone of patients with cancer, but in other disease populations, it appears that exercise could prevent the increase of angiotensin-converting enzyme and plasma angiotensin II levels (Nunes-Silva et al., 2017) (**Figure 7**).

The type of exercise and the intensity of exercise could be the important factors to consider for the PNS activation. First, to increase catecholamine production, moderate- or high-intensity exercise is needed (Zouhal et al., 2008). Additionally, in HF values, no significant differences between the control and the Qigong group were found (Lee et al., 2018), and the Tai Chi intervention presented the lowest MDs results (Zhou et al., 2018), which could mean that the intensity performed was too low to impact the PNS activity. Accordingly, low responses were also shown in the intervention in the study of Niederer et al. (2013), where participants engaged in unsupervised physical activity without a structured program (36). Still, studies carried out with other target populations show that low-intensity exercise modalities such as Tai Chi increased the parasympathetic stimulation (Cole et al., 2016). However, a study with elderly women, which compared the effects of the autonomic modulation of Tai Chi and walking programs, found no significant HRV differences between the groups (Audette et al., 2006). Perhaps higher intensities may be needed to increase the muscle recruitment associated with the rise in circulating catecholamines (Spiering et al., 2008), which has been shown to decrease HRV (Zouhal et al., 2008). Moreover, the comparison between the effects of endurance training and resistance training on the autonomic modulation, measured by HRV, is still controversial in patients with chronic diseases (Boudet et al., 2017). Although endurance training seemed to be more effective in modifying the HRV activity in healthy populations, in patients with metabolic syndrome, the high-intensity resistance training together with endurance seemed to have greater decreases in the heart rate and greater increases in the VLF domain compared with moderate resistance training with endurance workout (Boudet et al., 2017). These improvements could be produced by the role of strength training in declining the inflammatory process, an aspect shared with cancer physiology (Gleeson et al., 2011). Besides, resistance training may be utilized to prevent or to regain the decline of HRV considering that sarcopenia is a significant predictor of toxicity and time to tumor progression (Prado et al., 2009). More investigation is needed to identify the type of optimal exercise and to analyze the physiological process of resistance exercise in HRV physiology.

Most of the sport science investigations performed about HRV measure the effects of acute doses of exercise during the practice and in the recovery phase. In cancer, the acute effects of exercise have been analyzed with HF and RMSSD measures during and after yoga practice obtaining significant HF alterations in all the positions performed except in meditation and post-resting (Mackenzie et al., 2014). Hence, in line with the previous literature, a higher muscle activation may be required during exercise to stimulate the vagal nerve activity. An intervention carried out with Tai Chi Qigong added that a minimum of 4 min of practice is required to achieve the effects in HF and LF (Fong et al., 2015). Moreover, HRV measures could provide an opportunity to record how participants have responded to training in the 12–24 h post-exercise session (Javaloyes et al., 2020). These HRV outcomes, usually measured by RMSSD, can guide to decide the intensity and volume of the following session of training (Kiviniemi et al., 2007; Javaloyes et al., 2020). Nevertheless, no investigations have been performed at present with patients with cancer.

The current meta-analysis and systematic review are the first to explore the effects of exercise programs on the HRV of patients with cancer and its survivors. Some limitations need to be mentioned. The total sample size was moderate at best, although interventions that involved all types of exercise were included. Consequently, the studies analyzed were heterogeneous, limiting the generalization of the results, but still provide a wider review of the types of interventions investigated in the field. Finally, only studies written in English or Spanish, indexed in PubMed or Web of Science and articles with a before and after HRV measure or changes from baseline outcomes were included.

CONCLUSION

Exercise programs may lead to positive effects on the overall autonomic control, measured by HRV of patients with cancer and its survivors. This systematic review and meta-analysis show that exercise can increase SDNN (overall HRV), RMSSD, and HF (n.u. and ms^2), reflecting the stimulation of PNS activity. Furthermore, significant differences between EG and CG were also found in the LF and the LF/HF ratio of HRV variables. Due to the low number of interventions performed on HRV, exercise, and cancer, no further conclusions can be made. Thus, future research is needed to contrast the findings and to provide more specific information about the type and intensity of exercise required to improve the overall autonomic control and to reduce the toxicity and future autonomic dysfunction of the patient with cancer.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

AL-P, DC-M, and XM: conceptualization, resources, validation, and writing the original draft preparation. AL-P, DC-M, and AJ: methodology, writing the review, and editing. AL-P and DC-M: software, formal analysis, and data curation. GL, LH, and AJ: investigation. GL, LH, and XM: supervision. DC-M and AJ: project administration. All authors have read and approved the published version of the manuscript.

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