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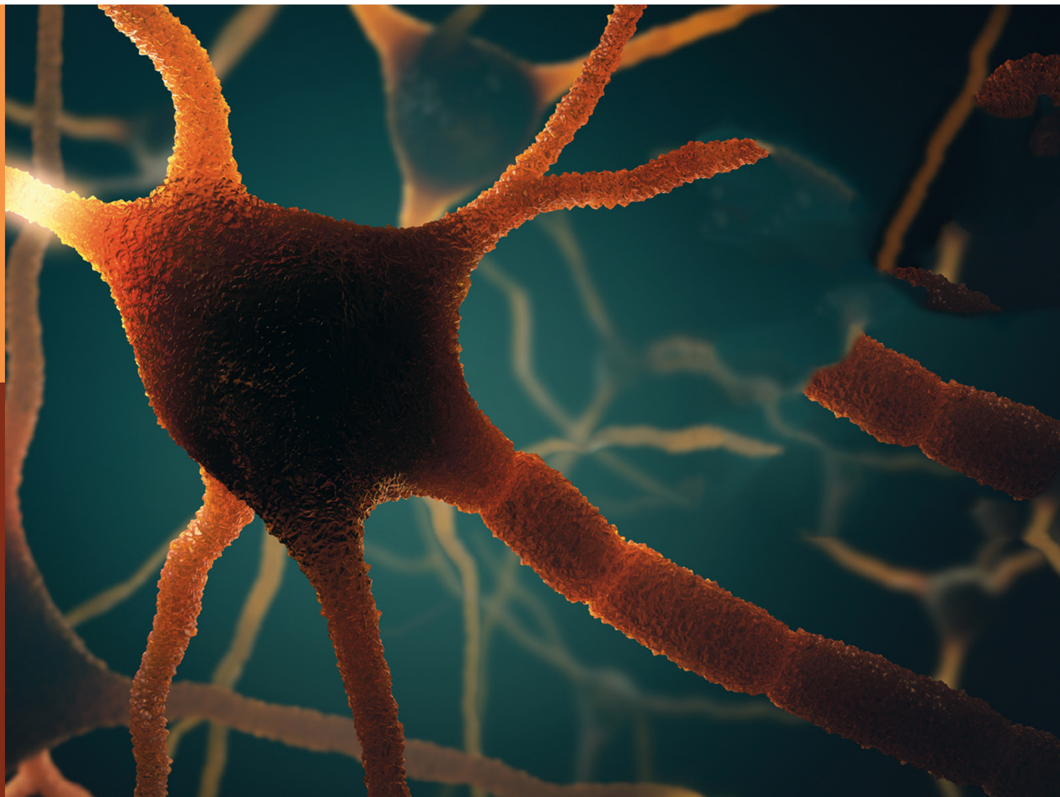

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Two for the price of one – effects and underlying mechanisms of combined motor-cognitive interventions on the body and the brain

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Table of contents

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CLINICAL TRIAL
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The Benefits of High-Intensity Interval Training on Cognition and Blood Pressure in Older Adults With Hypertension and Subjective Cognitive Decline: Results From the Heart & Mind Study

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Background: The impact of exercise on cognition in older adults with hypertension and subjective cognitive decline (SCD) is unclear.

Objectives: We determined the influence of high-intensity interval training (HIIT) combined with mind-motor training on cognition and systolic blood pressure (BP) in older adults with hypertension and SCD.

Methods: We randomized 128 community-dwelling older adults [age mean (SD): 71.1 (6.7), 47.7% females] with history of hypertension and SCD to either HIIT or a moderate-intensity continuous training (MCT) group. Both groups received 15 min of mind-motor training followed by 45 min of either HIIT or MCT. Participants exercised in total 60 min/day, 3 days/week for 6 months. We assessed changes in global cognitive functioning (GCF), Trail-Making Test (TMT), systolic and diastolic BP, and cardiorespiratory fitness.

Results: Participants in both groups improved diastolic BP [$F_{(1, 87.32)} = 4.392$, $p = 0.039$], with greatest effect within the HIIT group [estimated mean change (95% CI): −2.64 mmHg, (−4.79 to −0.48), $p = 0.017$], but no between-group differences were noted ($p = 0.17$). Both groups also improved cardiorespiratory fitness [$F_{(1, 69)} = 34.795$, $p < 0.001$], and TMT A [$F_{(1, 81.51)} = 26.871$, $p < 0.001$] and B [$F_{(1, 79.49)} = 23.107$, $p < 0.001$]. There were, however, no within- or between-group differences in GCF and systolic BP at follow-up.

Conclusion: Despite improvements in cardiorespiratory fitness, exercise of high- or moderate-intensity, combined with mind-motor training, did not improve GCF or systolic BP in individuals with hypertension and SCD.

Clinical Trial Registration: ClinicalTrials.gov (NCT03545958).

Keywords: exercise, aging, elderly, cardiovascular risk, memory impairment

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INTRODUCTION

Hypertension is associated with cognitive impairment in older adults (Iadecola et al., 2016), contributing heavily to cerebrovascular (Dichgans and Leys, 2017) and Alzheimer's disease pathophysiology (Rodrigue et al., 2013). Healthy older adults with subjective cognitive decline (SCD) may experience subtle cognitive deterioration due to brain pathology accumulating years before clinical diagnoses (Buckley et al., 2015). Individuals with history of both hypertension and SCD may be at higher risk of dementia because of increased cerebrovascular disease and neurodegenerative burden (Uiterwijk et al., 2014). Despite greater risk, the effects of non-pharmacological interventions to ameliorate cognition in these individuals remain unknown.

Exercise has been associated with improved cognition (Lautenschlager et al., 2008), and has been shown to positively impact both brain function (Voss et al., 2010) and structure (Erickson et al., 2011) in older adults, but evidence is limited in those with hypertension (Smith et al., 2010). High-intensity interval training (HIIT) is a modality of exercise training that yields similar or greater cardiorespiratory fitness improvements compared to conventional, moderate-intensity continuous training (MCT) (Wisløff et al., 2007). In clinical populations, HIIT has been shown to lower blood pressure (BP) to a greater extent compared to MCT, including within hypertensive patients (Pescatello et al., 2015). The effects of HIIT on cognition in older adults is understudied, as most trials have employed only MCT protocols (Northey et al., 2017). Further, with growing interest on multidomain interventions to improve cognition (Kivipelto et al., 2018), combining HIIT with mind-motor training approaches seems appealing. Square-stepping exercise (SSE) (Shigematsu et al., 2008) is a novel type of mind-motor training associated with positive effects on cognition (Gill et al., 2016); however, SSE has yet to be studied in individuals with hypertension and SCD.

In this study, we investigated the effects of combining HIIT with SSE on cognition and BP in older adults with a history of hypertension and SCD. We hypothesized that HIIT plus SSE would yield superior improvements in both BP and cognition outcomes compared to an active control group.

METHODS

Study Design and Participants

We conducted a 6-month, single-blind, two-arm randomized controlled trial based in the community following a pragmatic approach (Ford and Norrie, 2016). Participants were randomized to either intervention (HIIT) or comparator (MCT) groups. Randomization (1:1) was conducted via www.randomization.com with randomly selected block sizes (e.g., 4, 6, 8) (Friedman et al., 2010). Block randomization was used to avoid statistical challenges posed by clustering with simple randomization or sample size imbalance and loss of power (Friedman et al., 2010), while ensuring similar sample sizes in both groups at every 4, 6, or 8 blocks. Each participant had a 50% chance of being randomized to either group. No demographic characteristics or other factors were considered in the randomization procedure.

We included individuals who met the following criteria: (1) 55 years of age or older; (2) presented with a history of controlled or uncontrolled stage 1 hypertension, or taking antihypertensive BP medication (Leung et al., 2017); (3) had preserved instrumental activities of daily living (scoring >6/8 on the Lawton-Brody Instrumental Activities of Daily Living scale (Lawton and Brody, 1969)]; (4) presented with signs of SCD (defined as answering yes to the question: "Do you feel like your memory or thinking skills have gotten worse recently?"), as employed in previous exercise studies (Barnes et al., 2013); (5) preserved objective cognitive performance defined by scoring ≥26 on the Montreal Cognitive Assessment (MoCA) (McLennan et al., 2011) combined with study physician consult; and (6) able to comprehend the study letter of information and provide written informed consent.

Participants were excluded if they presented with: (1) significant neurological conditions or psychiatric disorders (e.g., diagnosis of Alzheimer's disease or vascular dementia, Parkinson's disease, stroke <1 year prior); (2) history of severe cardiovascular conditions [e.g., recent (<1 year) myocardial infarction] or symptomatic cerebrovascular disease; (3) significant orthopedic conditions; or (4) untreated clinical depression (i.e., score >15 on the Centers for Epidemiologic Studies Depression scale (Lewinsohn et al., 1997) combined with study physician consult). Participants were also excluded for any other factors that could potentially limit their ability to fully participate in the study.

All research participants provided written informed consent prior to partaking in any of the research activities. The Western Health Sciences Research Ethics Board approved the study and the trial was registered within ClinicalTrials.gov (NCT03545958) on May 22, 2018.

Interventions

Participants in both groups engaged in a 60-min, group-based, combined exercise program. Each session began with 15 min of mind motor training (i.e., SSE) followed by 45 min of either HIIT or MCT. The interventions were conducted with ≤30 participants/session, 3 days/week on non-consecutive days, for 6 months at the local YMCA. Participants used stationary bikes during HIIT or MCT and were coached by qualified fitness instructors with student volunteer assistance. Exercise intensity during HIIT and MCT was prescribed individually using training heart rate (HR), determined via exercise testing (see *"Cardiorespiratory fitness"* subsection) (American College of Sports Medicine, 2014). Intensity was monitored using chest-based HR monitors with a group tracking system (Myzone™) and via the modified 10-point Borg Rating of Perceived Exertion (RPE) scale (Borg, 1982). To increase motivation and ensure compliance with intensity protocol, each participant individual HR and % of HRmax achieved were continuously displayed to participants on a large screen during the exercise sessions. Intensity was stimulated via continuous increments in speed and/or resistance on the stationary bikes.

Mind-Motor Training

The SSE program is a group-based, visuospatial working memory task with a stepping response (see **Figure 1**) (Shigematsu et al., 2008). The training protocol entails the reproduction of complex stepping patterns on a gridded floor mat (2.5 m × 1 m). The stepping patterns are demonstrated by an instructor and participants are expected to memorize and then attempt to reproduce each pattern. The complexity of these patterns is based on the number of steps, order and direction of foot placement on the mat. Complexity was increased gradually in each session with the introduction of new patterns once 80% of participants had learned and repeated each pattern twice. The SSE sessions were conducted in groups ≤6 participants/mat, and participants were encouraged to assist each other by providing visual and verbal cues.

High-Intensity Interval Training

Each HIIT session was composed of a 5 to 10-min warm-up, a 25-min main activity, and a 5 to 10-min cool down. The 25-min main activity included 4 bouts of different exercise intensities (Molmen-Hansen et al., 2012). In each bout, participants received 4 min of high-intensity cycling (starting at 80–90% HRmax, and progressing toward 85–95% HRmax) followed by 3 min of active rest (aiming for 40–60% HRmax) (Molmen-Hansen et al., 2012). This HIIT protocol was deemed safe to be implemented in our study as it was originally designed to reduce systolic (SBP) in patients with essential hypertension at baseline (Molmen-Hansen et al., 2012), and has been safely applied to several other clinical populations (Mezzani et al., 2012). Exercise intensity was monitored throughout the HIIT sessions with volunteers collecting HR and RPE once during warm-up and cool-down, as well as during each active and rest period. Participants were verbally encouraged by instructors to achieve the prescribed exercise intensity in each high-intensity, 4-min active period. Progression was made gradually over the course of the study during each session until participants were able to comfortably reach and/or maintain the high-intensity training zone (i.e., 80–95% HRmax) during the active high-intensity periods.

Moderate-Intensity Continuous Training

Each MCT session consisted of a 5 to 10-min warm-up, a 25-min continuous cycling at moderate-intensity (starting at 60–80% HRmax) component, and a 5 to 10-min cool down. Exercise intensity was monitored throughout the MCT sessions with volunteers collecting HR and RPE once during warm-up and cool-down, and every 5 min within the 25-min main component. Participants were also encouraged verbally by instructors to maintain their HR within the moderate-intensity training zone during each exercise session (i.e., 60–80% HRmax).

Measurements

Participants attended baseline measurements prior to study randomization (i.e., blind baseline assessments). We collected clinical and demographic information, and performed cardiovascular, cardiorespiratory and cognitive assessments over 2 days. Baseline and 6-month follow-up measurements were conducted by trained assessors; at follow-up, assessors were blinded to group allocation for assessment of BP and cognition. All follow-up measurements were performed within 1–2 weeks after the end of the study intervention.

Cognition Assessment

Global cognitive functioning (GCF) was the primary outcome of this study, derived from the Cambridge Brain Sciences (CBS) battery (Hampshire et al., 2012). The CBS battery contains 12 non-verbal, culturally independent cognitive tasks covering four broad cognitive domains (i.e., memory, reasoning, concentration, and planning, see details in **Supplementary Methods**) (Hampshire et al., 2012). It is a fully automated, computerized adaptive testing platform and has been used to effectively evaluate cognition in several large-scale studies (Wild et al., 2018). The tasks were conducted using laptops with access to internet provided by study personnel. Before each task, participants practiced with a tutorial under the guidance of a trained assessor. Assessors provided assistance as necessary but were instructed not to intervene once participants completed the tutorial and data collection began. The outcome measure was derived based on participant scores on each of the 12 CBS tasks. Following previous methods (Gill et al., 2016), task scores were z-transformed and averaged to create domain-specific composite scores. These composite scores were then averaged to create a GCF score, used as the primary outcome. Domain-specific scores were retained for secondary analysis. Additionally, we administered the paper-based Trail-Making Test (TMT) to assess changes in lower-level cognitive processes (e.g., processing speed, set-shifting) (Reitan, 1992). This measure was included since it is a commonly used test in exercise studies due to its sensitivity to capture the effects of exercise on cognition in older adults (Boa Sorte Silva et al., 2020a).

Blood Pressure Assessment

Automated office SBP was the co-primary outcome in this study. Measurements were obtained by trained technicians with an automated monitor (Watch BP Office, Microlife AG, Switzerland), with standardized cuff size and position. The left arm was preferred for BP assessments across all participants whenever possible (i.e., exceptions were severe discomfort caused by muscle injuries or scar tissue from previous surgeries). Nonetheless, the same arm was used for both baseline and follow-up assessments to ensure consistency within participants. After a 5-min seated resting period, BP was collected four times with 1-min intervals (Leung et al., 2017). The first BP measurement was discarded and the average of the last three SBP readings were used for analysis. We also retained the last three measures of diastolic BP (DBP) and resting HR as secondary outcomes. We performed BP measurements within 1–2 weeks after the end of the study intervention but no earlier than 24 h after the last exercise session attended by the study participants. Furthermore, to minimize the influence of other external factors, participants were asked to take their medication as usual, refrain from alcohol consumption and vigorous exercise 24 h prior to assessment, refrain from caffeine intake on the day of assessment, and were asked void their bladder before BP measurements.

FIGURE 1 | Participants performing the square-stepping exercise.

Cardiorespiratory Fitness

We conducted maximal exercise testing (Gibbons et al., 1997) using a treadmill (Quinton® TM55) connected to a desktop computer equipped with the Q-Stress™ Cardiac Science™ software, Version 4.5 (Cardiac Science Corp., USA). The maximal test ended once participants had subjectively reached their maximum capacity and asked for the test to be stopped. The test was also ended under the study physician's recommendations. We monitored HR via exercise echocardiogram (ECG) with electrodes (10-lead) connected to participant's chest. The Bruce (Bruce et al., 1973) treadmill test was applied in this study and we retained time to exhaustion, estimated metabolic equivalent (MET), and HRmax for secondary outcome analysis.

Samples Size

A meta-analysis (Colcombe and Kramer, 2003) suggested that exercise improves cognition with an overall effect size of $d = 0.48$. Further, Cornelissen and Fagard (2005) reported that exercise training is associated with an overall 6.9 mmHg reduction in SBP hypertensive patients, with an effect size of $d = 0.85$ (Morris, 2008). Considering a greater effect of exercise on SBP, we estimated our sample size using an approximate effect size for cognition. Based on this, with 63 participants per group, our study would have 80% power at the 5% significance level to detect a moderate effect size of $d = 0.55$ (Lachin, 1981). We estimated a dropout rate of 20% during the 6-month period, which increased our calculation to 70 participants per group. This proposed sample size is in line with previous investigations (Lautenschlager et al., 2008).

Statistical Analyses

We analyzed the outcome data based on an intent-to-treat approach, using linear mixed effects regression models for repeated measurements (LMM) (Fitzmaurice et al., 2004). We included all randomized participants, regardless of missing data at follow-up (Fitzmaurice et al., 2004). Time was considered as a repeated, categorical variable included as a fixed effect in addition to group and group-by-time interaction (Fitzmaurice et al., 2004). For primary outcomes, we examined the difference between groups in estimated mean change in GCF and SBP from baseline to 6 months.

For our secondary outcomes, we examined changes in domain-specific cognition (i.e., memory, reasoning, concentration, and planning), TMT parts A and B, cardiovascular outcomes (i.e., office DBP and resting HR), and cardiorespiratory fitness (i.e., time to exhaustion, METs achieved and HRmax). We also conducted sensitivity analyses adjusting for age, sex, MoCA scores, baseline cardiorespiratory fitness (i.e., time to exhaustion), as well as history and/or medication use for diabetes, cardiovascular disease (including hypertension), and depression.

Furthermore, to handle missing data and perform confirmatory analysis in both primary outcomes, we first conducted complete-case analysis including only participants who completed baseline and 6-month assessment. Second, we used multiple imputation under the assumption that data were missing at random [Little's MCAR test: $\chi^2(137) = 159.99$, $p = 0.087$]. Following previous methods (Ten Brinke et al., 2020), we created 40 imputed datasets using random number generation and repeated the LMM for both GCF and SBP. The results of each LMM were pooled across all imputed datasets.

Additionally, we used *post-hoc* analyses to investigate subgroup effects on primary outcomes based on sex, and baseline median values for SBP and cardiorespiratory fitness (i.e., time to exhaustion). We based our interpretation of study results on estimation and associated 95% confidence intervals (CI). For all subgroup analyses, we adjusted p using the Benjamini-Hochberg false discovery rate approach (Benjamini and Hochberg, 1995), with an adjusted significance threshold $p \leq 0.005$.

Analyses were performed on IBM® SPSS® Statistics, Version 24 (IBM Corp, USA), and R, Version 3.6.1 (http://www.R-project.org).

RESULTS

Enrollment and Adherence

Participant flow during the study is shown **Figure 2**. The study period ran between July 2018 and March 2020. Participant demographic information and clinical characteristics are presented in **Table 1**, while baseline outcome measures are reported in **Table 2**. Overall, at baseline, participants included ($n = 128$) had preserved cognitive function (McLennan et al., 2011), were mostly Caucasian, highly educated (**Table 1**), and had "greater than average" cardiorespiratory fitness (Mandsager et al., 2018) compared to normative data (see **Table 2**). Average attendance to the exercise sessions was 54% for the MCT group and 51% for the HIIT group, with no differences between groups [$t_{(126)} = 0.45$, $p = 0.65$].

Adherence to exercise intensity was monitored using %HRmax and RPE data collected during the exercise sessions. **Figure 3** demonstrates average exercise intensity for both HIIT and MCT groups in each exercise session. The data indicate that both groups exercised at different intensities as prescribed in the study protocol, with participants in the HIIT group exercising at higher intensities [mean (standard deviation), %HRmax = 85.01 (6.93), RPE = 6.29 (1.24)] compared to those in the MCT group [%HRmax = 75.91 (6.28), RPE = 4.68 (1.20)]. An independent samples t-test comparing average exercise intensity achieved by each participant across all exercise sessions revealed that indeed the HIIT group performed at higher intensity as indexed by %HRmax [$t_{(110)} = 7.28$, $p < 0.001$] and RPE [$t_{(110)}, = 7.00$, $p < 0.001$] data collected.

Outcomes

Main results (intention-to-treat approach) are shown in **Table 3**. Complete-case and multiple-imputation data analysis revealed similar results (see **Supplementary Table 1**).

Cognition

There were no significant within- or between-group differences in GCF or any of the domain-specific composite scores at 6 months (see **Table 3** and **Figures 4**, **5**); sensitivity analyses indicated that results remained unchanged in fully adjusted models (**Table 3**). While there were no differences between

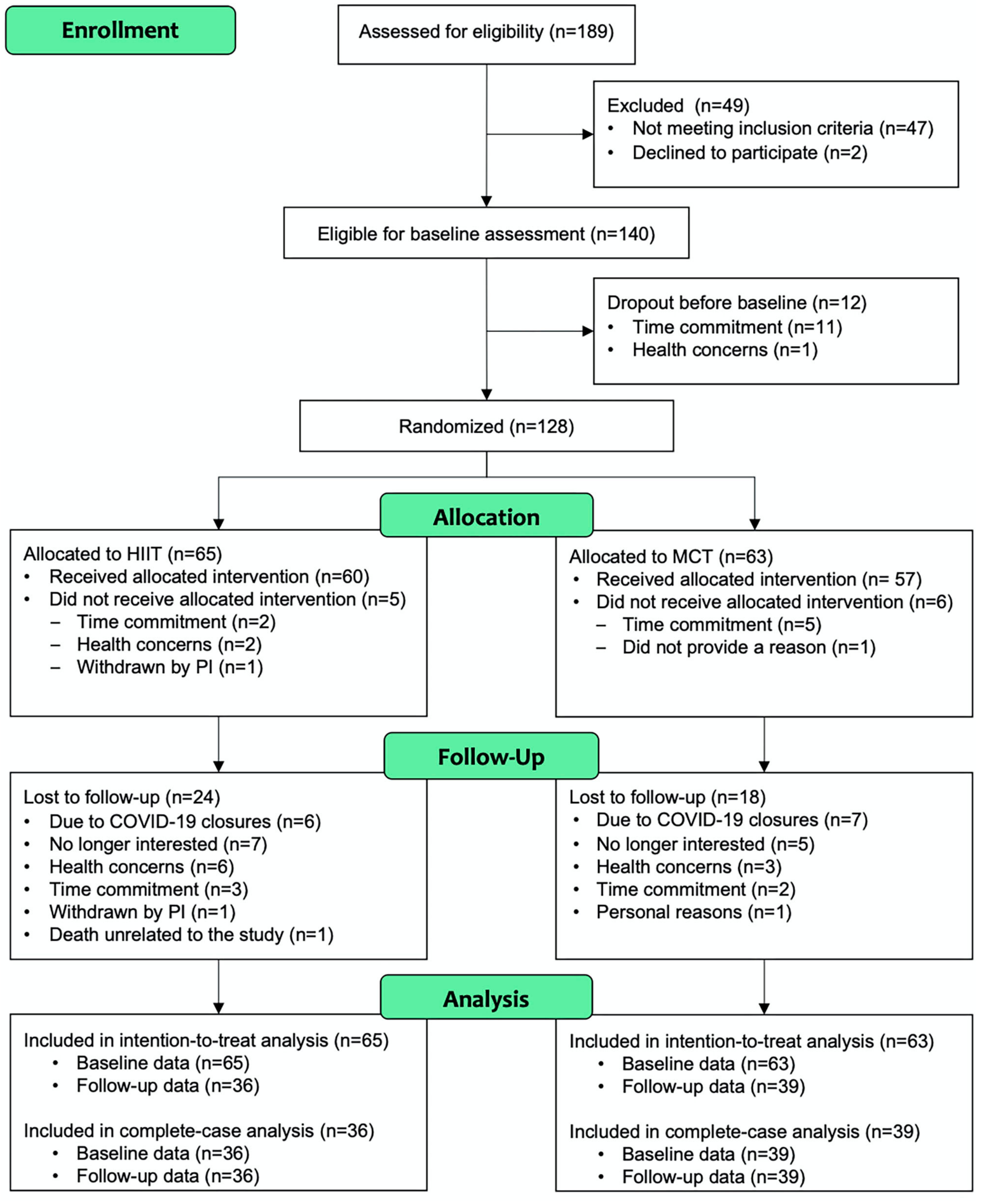

FIGURE 2 | Study CONSORT diagram to illustrate participant flow throughout the study.

TABLE 1 | Participant demographics and clinical characteristics.

Baseline descriptors[a]	**HIIT ($n = 65$)**	**MCT ($n = 63$)**	**Total ($n = 128$)**	***p*-value**[b]
Demographics				
Age, yr	71.7 (6.3)	70.4 (7.1)	71.1 (6.7)	0.27
Females, *n* (%)	32 (49.2)	29 (46.0)	61 (47.7)	0.85
Caucasian, *n* (%)	56 (86.2)	57 (90.5)	113 (88.3)	0.76
Education, yr	16 (3.2)	16.6 (3.6)	16.3 (3.4)	0.38
MoCA, score	26.9 (1.6)	26.8 (1.5)	26.8 (1.6)	0.81
MMSE, score	29.2 (1.1)	29.2 (1.0)	29.2 (1.0)	0.96
CES-D, score	9.0 (7.3)	8.8 (7.1)	8.9 (7.2)	0.83
IADL	7.9 (0.3)	7.9 (0.3)	7.9 (0.3)	
Height, cm	166.7 (9.2)	167.7 (11.3)	167.2 (10.3)	0.57
Weight, kg	81.5 (17.1)	85.4 (21.5)	83.4 (19.4)	0.25
BMI, kg/m^2	29.3 (5.8)	30.3 (6.5)	29.8 (6.2)	0.38
Diagnosed comorbidities, *n* (%)				
Hypertension	51 (78.5)	49 (77.8)	100 (78.1)	1.00
Arthritis	23 (35.4)	25 (39.7)	48 (37.5)	0.75
Diabetes	11 (16.9)	13 (20.6)	24 (18.8)	0.76
Depression	4 (6.2)	12 (19.0)	16 (12.5)	0.053
Medication usage, *n* (%)				
Blood pressure	53 (81.5)	53 (84.1)	106 (82.8)	0.88
Cholesterol	31 (47.7)	33 (52.4)	64 (50.0)	0.72
Diabetes	9 (13.8)	13 (20.6)	22 (17.2)	0.43
Depression	6 (9.2)	11 (17.5)	17 (13.3)	0.27
Arthritis	6 (9.2)	5 (7.9)	11 (8.6)	1.00
Blood thinners	3 (4.6)	4 (4.8)	7 (5.5)	0.97

[a]Data presented as mean (standard deviation) unless otherwise indicated. [b]Significance for independent samples t-test for continuous variables, or Chi-square test for independence for categorical variables. HIIT, high-intensity interval training; MCT, moderate-intensity continuous training; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; CES-D, Center for Epidemiologic Studies Depression Scale; IADL, Instrumental Activities of Daily Living Scale.

TABLE 2 | Study baseline measures.

Baseline outcomes[a]	**HIIT ($n = 65$)**	**MCT ($n = 63$)**	**Total ($n = 128$)**	***p*-value**[b]
Cognition, z score				
GCF	0.004 (0.553)	−0.004 (0.594)	0 (0.571)	0.94
Memory	−0.03 (0.609)	0.031 (0.695)	0 (0.651)	0.60
Concentration	−0.01 (0.745)	0.01 (0.752)	0 (0.746)	0.88
Planning	0.031 (0.791)	−0.032 (0.839)	0 (0.812)	0.66
Reasoning	0.023 (0.668)	−0.024 (0.739)	0 (0.702)	0.71
Blood pressure, mm Hg				
Systolic	129.8 (16.0)	128.8 (16.0)	129.3 (15.9)	0.73
Diastolic	73.3 (8.3)	72.8 (8.7)	73.1 (8.5)	0.75
Trail-Making Test, s, median (IQR)				
Part A	36.0 (28.0, 44.0)	32.0 (28.0, 41.7)	34.5 (28.0, 43.0)	0.39
Part B	65.0 (49.0, 94.5)	68.0 (49.0, 92.0)	65.2 (49.0, 92.75)	0.81
Cardiorespiratory fitness[c]				
Time to exhaustion, min	7.0 (2.3)	6.9 (2.2)	6.9 (2.2)	0.93
Maximum intensity, METs	8.6 (2.4)	8.6 (2.2)	8.6 (2.3)	0.97
Maximum heart rate, bpm	144.2 (18.4)	144.9 (18.8)	144.5 (18.5)	0.85

[a]Data presented as mean (standard deviation) unless otherwise indicated. [b]Significance for independent samples t-test for continuous variables. [c]Exercise stress test data available from 118 (HIIT = 62, MCT = 56). HIIT, high-intensity interval training; MCT, moderate-intensity continuous training; GCF, global cognitive functioning; IQR, interquartile range; METs, metabolic equivalent.

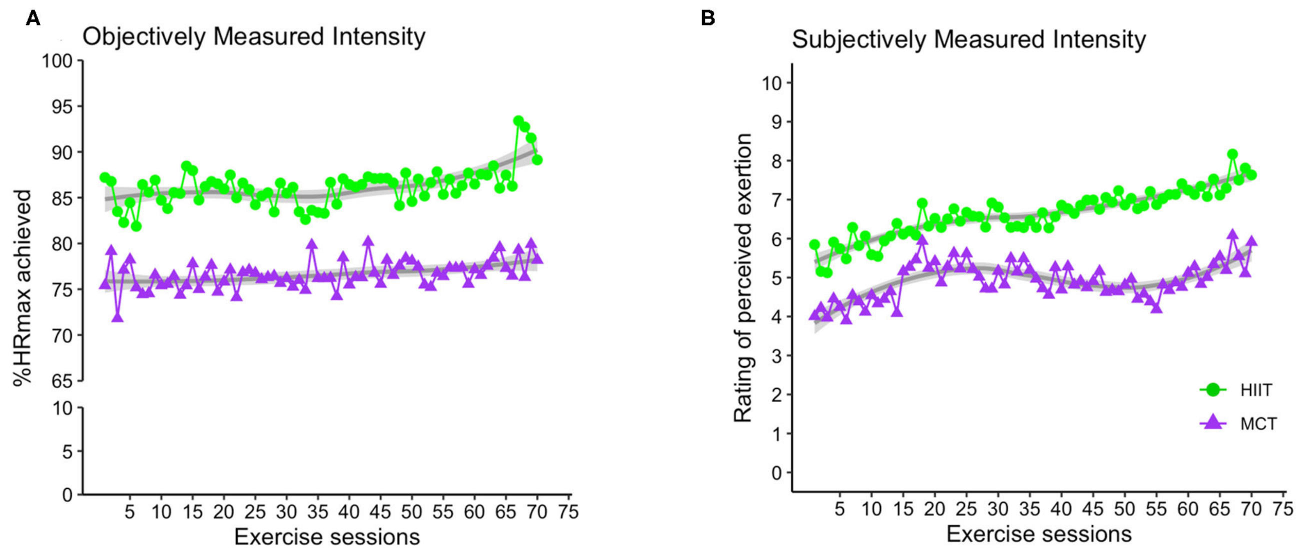

FIGURE 3 | Group average for exercise intensity achieved over the course of the exercise sessions as indexed by %HRmax **(A)** and RPE **(B)**. For the HIIT group, data shown represent average exercise intensity at the 2-min mark within each 4-min bout of HIIT exercise. For MCT group, the data indicate average exercise intensity collected at 4 different timepoints within the each MCT session (i.e., at 5, 10, 20, and 25 min during the main MCT component, i.e., after 5 to 10 min of warm-up). %HRmax, percentage of maximum heart rate; RPE, rating of perceived exertion; HIIT, high-intensity interval training; MCT, moderate-intensity continuous training.

groups, we did observe improvements in both groups in processing speed [$F_{(1, 81.51)} = 26.871$, $p < 0.001$] and mental flexibility/executive functioning [$F_{(1, 79.49)} = 23.107$, $p < 0.001$] measured using the paper-based TMT A and B, respectively. Nonetheless, the more complex TMT set-shifting score (Part A-B) did not change over time in either group (see **Table 3**). These findings for TMT A and B remained significant in fully adjusted models [Part A: $F_{(1, 89.65)} = 21.572$, $p < 0.001$, and Part B: $F_{(1, 86.84)} = 10.947$, $p < 0.001$].

Blood Pressure

No significant changes were seen for SBP or resting HR and results remained unchanged in fully adjusted models. Both groups improved DBP at follow-up [$F_{(1, 87.32)} = 4.392$, $p = 0.04$], and while changes were driven by a greater reduction in the HIIT group, the between-group difference did not reach statistical significance. Change in DBP remained significant for the HIIT group [estimated mean change (95% CI): −2.41 mmHg, (−4.69 to −0.12), $p = 0.039$] in fully adjusted models (**Table 3)**]. We repeated our analysis excluding 9 participants who had changes in their BP medication and found that DBP changes remained significant within the HIIT group [estimated mean change (95% CI): −2.47 mmHg, (−4.83 to −0.10), $p = 0.041$, $n = 119$]. Further subgroup analyses revealed reduction in SBP for HIIT participants with high SBP at baseline (i.e., those with SBP ≥ 128 mmHg). This improvement was statistically superior compared to participants with low BP in both HIIT and MCT subgroups at the adjusted significance threshold ($p \leq 0.005$), see **Figure 6**.

Cardiorespiratory Fitness

Cardiorespiratory fitness improved in both groups at follow-up as demonstrated by a greater time to exhaustion [$F_{(1, 69)} = 34.795$, $p < 0.001$, **Figure 7**] and METs achieved [$F_{(1, 69.84)} = 22.303$, $p < 0.001$]; however, no between-group differences were noted. Results remained significant in fully adjusted models for time to exhaustion [$F_{(1, 69.13)} = 35.985$, $p < 0.001$] and METs achieved [$F_{(1, 72.87)} = 21.841$, $p < 0.001$]. Subgroup analyses revealed that significant changes in time to exhaustion were driven by greater improvements among females within the MCT group and males within the HIIT group at adjusted significance threshold ($p \leq 0.005$, see **Figure 7**). Also, within group improvements at 6 months were driven mainly by enhanced performance on participant with greater fitness at baseline, see **Supplementary Table 4**).

Adverse Events

We documented 12 study-related adverse events, 6 in the HIIT group and 6 in the MCT group. These adverse events were low-back pain (5), hip soreness (2), hypertensive crisis (1), knee soreness (2), and muscle soreness (2), and were resolved within the duration of the study.

DISCUSSION

The goal of our study was to investigate the impact of a 6-month HIIT with mind-motor training intervention on vascular and cognitive outcomes, compared to an active control group, in older adults with history of hypertension and SCD.

The effectiveness of exercise to improve cognition in those with hypertension remains to be determined, as there is dearth of RCTs on aerobic exercise to improve cognition in older adults with hypertension. Pierce and colleagues conducted a 4-month RCT comparing the effects of aerobic exercise on

TABLE 3 | Within- and between-group differences from baseline to 6 months by randomization group.

Outcomes[a]		Within-group estimated mean change (95% CI)				Between-group differences (95% CI)	
		HIIT ($n = 65$)	***p* Value**	**MCT ($n = 63$)**	***p* Value**	**6 months ($n = 128$)**	***p* Value**
Cognition, z score							
GCF							
	Unadjusted	−0.02 (−0.12 to 0.08)	0.67	0.06 (−0.04 to 0.16)	0.23	−0.08 (−0.22 to 0.06)	0.25
	Adjusted	−0.03 (−0.14 to 0.08)	0.64	0.04 (−0.07 to 0.14)	0.48	−0.06 (−0.21 to 0.08)	0.38
Memory							
	Unadjusted	−0.02 (−0.18 to 0.14)	0.83	0.12 (−0.03 to 0.28)	0.11	−0.14 (−0.36 to 0.08)	0.20
	Adjusted	−0.004 (−0.17 to 0.16)	0.96	0.11 (−0.05 to 0.27)	0.19	−0.11 (−0.34 to 0.11)	0.31
Concentration							
	Unadjusted	−0.10 (−0.29 to 0.08)	0.28	0.08 (−0.10 to 0.25)	0.40	−0.18 (−0.43 to 0.08)	0.18
	Adjusted	−0.14 (−0.33 to 0.06)	0.18	0.05 (−0.15 to 0.24)	0.63	−0.18 (−0.45 to 0.08)	0.17
Planning							
	Unadjusted	0.02 (−0.21 to 0.25)	0.89	−0.04 (−0.26 to 0.18)	0.69	0.06 (−0.26 to 0.38)	0.71
	Adjusted	−0.04 (−0.28 to 0.21)	0.77	−0.04 (−0.28 to 0.20)	0.75	0.002 (−0.33 to 0.33)	0.99
Reasoning							
	Unadjusted	0.06 (−0.16 to 0.27)	0.60	0.14 (−0.06 to 0.35)	0.18	−0.08 (−0.38 to 0.21)	0.57
	Adjusted	0.05 (−0.18 to 0.27)	0.68	0.10 (−0.12 to 0.32)	0.39	−0.05 (−0.35 to 0.26)	0.76
Blood pressure							
Systolic, mmHg							
	Unadjusted	−2.58 (−6.62 to 1.46)	0.21	1.16 (−2.76 to 5.07)	0.56	−3.74 (−9.36 to 1.89)	0.19
	Adjusted	−0.24 (−4.52 to 4.04)	0.91	2.86 (−1.32 to 7.06)	0.18	−3.11 (−8.84 to 2.62)	0.28
Diastolic, mmHg							
	Unadjusted	**−2.64 (−4.79 to −0.48)**	**0.017**	−0.53 (−2.63 to 1.56)	0.62	−2.11 (−5.11 to 0.90)	0.17
	Adjusted	**−2.41 (−4.69 to −0.12)**	**0.039**	−0.47 (−2.71 to 1.78)	0.68	−1.94 (−5.01 to 1.13)	0.21
Resting heart rate, bpm							
	Unadjusted	−1.76 (−4.81 to 1.29)	0.26	0.54 (−2.40 to 3.48)	0.72	−2.3 (−6.53 to 1.94)	0.28
	Adjusted	−1.35 (−4.48 to 1.77)	0.39	1.19 (-1.86 to 4.24)	0.44	−2.54 (−6.72 to 1.64)	0.23
Trail-Making Test[b]							
Part A							
	Unadjusted	**−0.07 (−0.11 to −0.03)**	**<0.001**	**−0.07 (−0.10 to −0.03)**	**0.001**	−0.005 (−0.06 to 0.05)	0.86
	Adjusted	**−0.06 (−0.10 to −0.02)**	**<0.003**	**−0.07 (−0.11 to −0.03)**	**<0.001**	0.01 (−0.04 to 0.07)	0.69
Part B							
	Unadjusted	**−0.07 (−0.11 to −0.03)**	**0.001**	**−0.06 (−0.09 to −0.02)**	**0.002**	−0.01 (−0.06 to 0.04)	0.68
	Adjusted	**−0.06 (−0.10 to −0.01)**	**<0.009**	**−0.05 (−0.09 to −0.005)**	**0.029**	−0.01 (−0.7 to 0.04)	0.69
B minus A							
	Unadjusted	−0.002 (−0.05 to 0.05)	0.93	0.001 (−0.05 to 0.05)	0.97	−0.003 (−0.07 to 0.07)	0.93
	Adjusted	0.01 (−0.04 to 0.07)	0.64	0.03 (−0.03 to 0.08)	0.31	−0.01 (−0.09 to 0.06)	0.69
Cardiorespiratory fitness[c]							
Time to exhaustion, min							
	Unadjusted	**1.12 (0.63 to 1.62)**	**<0.001**	**0.93 (0.45 to 1.42)**	**<0.001**	0.19 (−0.51 to 0.88)	0.59
	Adjusted	**1.14 (0.64 to 1.63)**	**<0.001**	**0.95 (0.46 to 1.44)**	**<0.001**	0.19 (−0.51 to 0.88)	0.59
Intensity, METs							
	Unadjusted	**1.18 (0.58 to 1.78)**	**<0.001**	**0.83 (0.24 to 1.43)**	**0.007**	0.35 (−0.50 to 1.20)	0.42
	Adjusted	**1.14 (0.54 to 1.74)**	**<0.001**	**0.83 (0.24 to 1.42)**	**0.006**	0.31 (−0.53 to 1.15)	0.47
Maximum heart rate, bpm							
	Unadjusted	−0.24 (−4.91 to 4.42)	0.92	0.65 (−3.95 to 5.25)	0.78	−0.89 (−7.44 to 5.66)	0.79
	Adjusted	−0.29 (−4.95 to 4.36)	0.90	0.64 (−3.96 to 5.24)	0.78	−0.93 (−7.48 o 5.61)	0.78

[a]Calculated from linear mixed effects regression models that included group (HIIT or MCT), time (baseline and 6 months), and group × time interaction terms. Results are presented as intention-to-treat approach. Bold numbers indicate significant differences. Adjusted models account for the influence of age, sex, Montreal Cognitive Assessment score, baseline cardiorespiratory fitness, as well as history or medication use for diabetes, cardiovascular disease, and depression. [b]Log10 transformation applied. [c]Data available from 118 (HIIT = 62, MCT = 56). CI, confidence interval; HIIT, high-intensity interval training; MCT, moderate-intensity continuous training, GCF, global cognitive functioning; METs, metabolic equivalent.

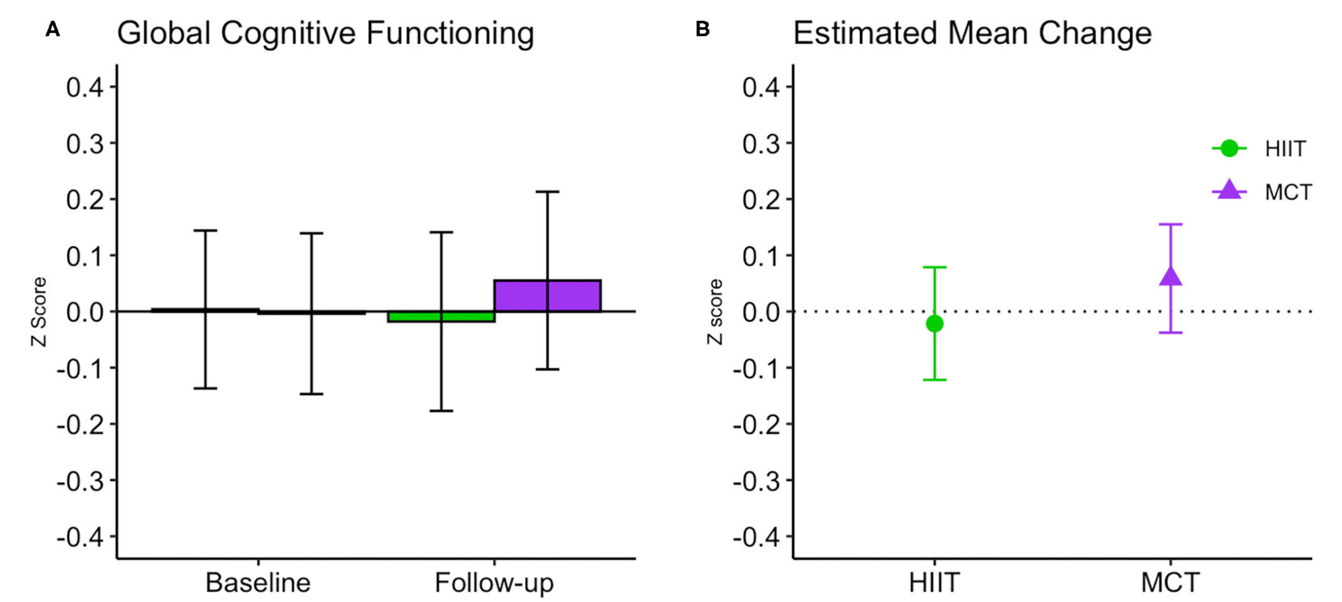

FIGURE 4 | Baseline and follow-up means for global cognitive function (**A**, group mean and 95% CI) and estimated mean change from baseline to 6 months (**B**, estimated mean change and 95% CI). CI, confidence interval; HIIT, high-intensity interval training; MCT, moderate-intensity continuous training.

measures of executive function, memory, and processing speed in hypertensive young and older adults (29–59 years of age) compared to strength training, or a wait-list control group (Pierce et al., 1993). No differences between groups were observed after the intervention in any outcome. In an RCT administering a 4-month, multi-domain lifestyle intervention (i.e., diet, exercise and caloric restriction) to young older adults with hypertension, Smith and colleagues reported that those who engaged in an exercise program in addition to diet and caloric restriction improved executive function, memory and learning compared to a usual care control group, with positive effects also in VO_2max and BP (Blumenthal et al., 2010; Smith et al., 2010). Taken together, these findings may suggest an additive benefit of aerobic exercise to cognition in adults with hypertension, however, due to fairly young samples involved in both RCTs and the uncertainty about the cognitive status of participants at baseline, their results may not be generalized to an older population of persons with hypertension and SCD. Also, these investigations only applied exercise protocols of MCT therefore, the effects of HIIT on cognition in this population has yet to be determined.

Our study is the first, to our knowledge, to investigate the impact of HIIT and mind-motor training on cognition and BP in older adults with a history of hypertension and SCD. Our assumptions were that by targeting BP control with HIIT and potentially amplifying cognitive improvements with supplementary mind-motor training, we would observe greater synergistic benefits to cognition. Strong evidence supports aerobic exercise as an effective therapy to lowering BP and managing hypertension (Pescatello et al., 2004). We hypothesized that these effects would, in turn, alleviate cerebrovascular burden and yield cognitive improvements and/or prevent decline (Baumgart et al., 2015). Despite lack of changes of GCF, our program did positively impact lower-level cognitive functioning measured via the TMT A and B, likely resulting from improved processing speed in both groups. Nonetheless, the more complex TMT set-shifting score (Part A-B) did not improve over time (Varjacic et al., 2018).

Our results indicated that the exercise program did not have the hypothesized effect on the study primary outcomes. At the end of the study, GCF remained unchanged despite improvements in cardiorespiratory fitness. Very few studies have conducted a similar investigation, with one trial reporting no changes in cognition in hypertensive middle-aged adults (Pierce et al., 1993). Therefore, it is plausible that our null findings on GCF signifies that hypertensive older adults with SCD may be less responsive to the benefits of HIIT and mind-motor training in higher-level cognitive functioning. This is possibly due to greater severity of hypertension burden on brain structure and function, which is prevalent in frontal-cortical and subcortical regions (Dichgans and Leys, 2017; Alber et al., 2019). This is reasonable considering that HIIT seems to impart benefits on memory in otherwise healthy older adults, as reported by Kovacevic et al. (2019) following a similar HIIT protocol. Another plausible explanation is that HIIT may not in fact be superior to MCT when assessing a range of different outcomes, including cognition, in older adults with a history of hypertension. Considering the recent findings of a systematic review and meta-analysis (Malmberg Gavelin et al., 2020), where small to medium effect sizes were observed for combined sequential exercise and cognitive training on cognition, it is also plausible that our study was underpowered to find significant effects.

We also reported no effects on SBP within or between groups. This finding was surprising and does not align with previous

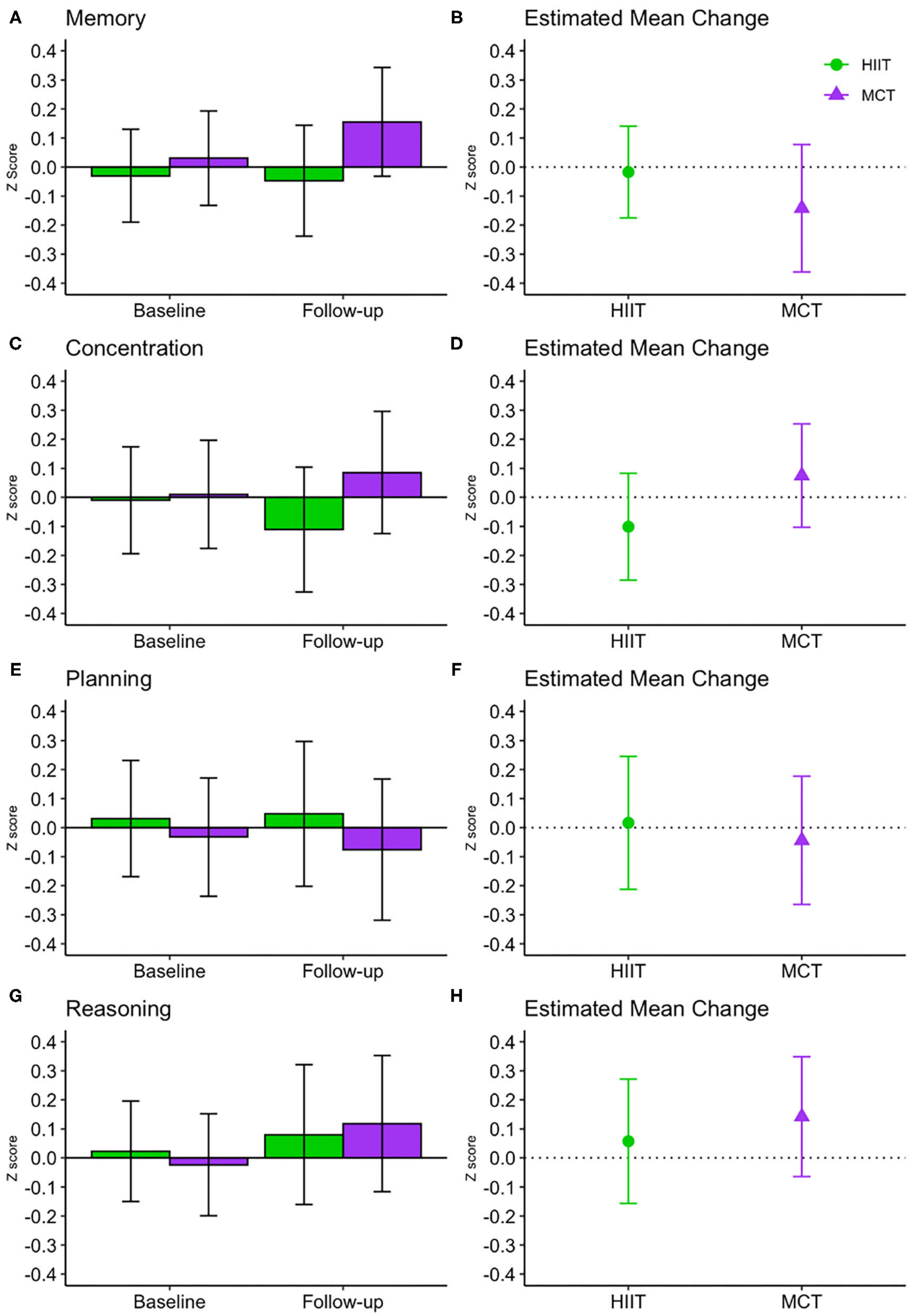

FIGURE 5 | Baseline and follow-up means for domain-specific cognitive function (**A,C,E,G**, show group mean and 95% CI) and estimated mean change from baseline to 6 months (**B,D,F,H** show estimated mean change and 95% CI). CI, confidence interval; HIIT, high-intensity interval training; MCT, moderate-intensity continuous training.

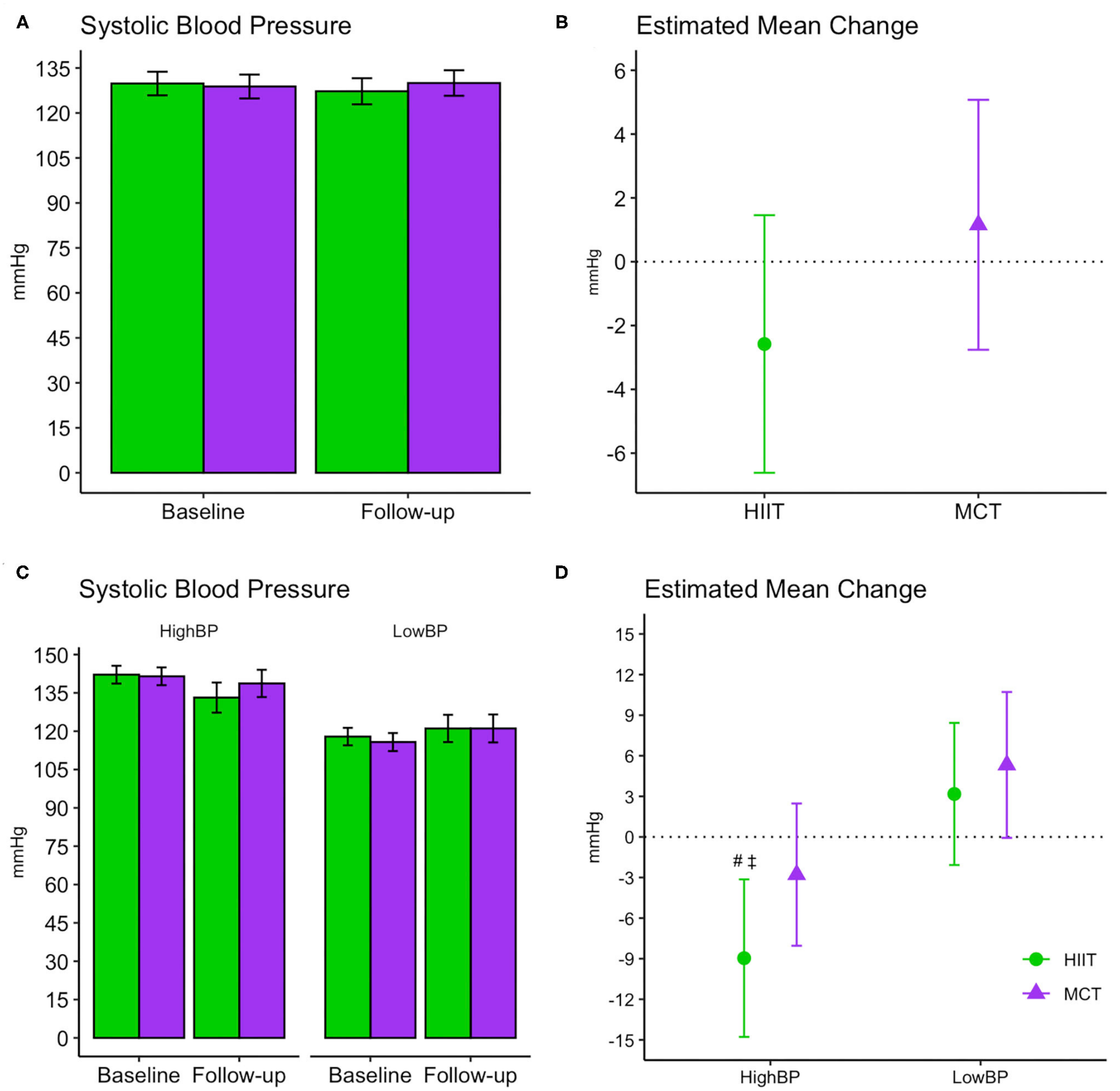

FIGURE 6 | Baseline and follow-up means for systolic blood pressure readings (**A,C**, group mean and 95% CI) and estimated mean change from baseline to 6 months (**B,D**, estimated mean change and 95% CI). **(A,B)** Display changes for the entire sample, while **(C,D)** display changes within subgroups stratified by baseline systolic blood pressure readings. #, significant changes over time at adjusted significance threshold ($p \leq 0.005$); See **Supplementary Table 2** for further details. ‡, greater changes compared to HIIT Low BP [difference between groups (CI): −12.14 mmHg (−19.98 to −4.30), $p = 0.003$] and MCT Low BP [−14.28 mmHg (−22.22 to −6.35), $p = 0.001$] at adjusted significance threshold ($p \leq 0.005$). CI, confidence interval; HIIT, high-intensity interval training; MCT, moderate-intensity continuous training; High BP, high systolic blood pressure at baseline; Low BP, low systolic blood pressure at baseline.

research on exercise and BP control in hypertensive patients (Molmen-Hansen et al., 2012; Pescatello et al., 2015). A plausible explanation for our BP results is that our sample included individuals with controlled and uncontrolled hypertension at study entry, which could have led to mixed response to our training protocol. Another investigation showed blunted SBP response in older adults with controlled hypertension following HIIT and MCT (Iellamo et al., 2014). Molmen-Hansen et al. (2012) reported significant SBP reduction in middle-aged adults following a similar HIIT protocol, and their sample only included individuals with uncontrolled BP at baseline. Our subgroup analysis offered confirmation to this hypothesis with HIIT having

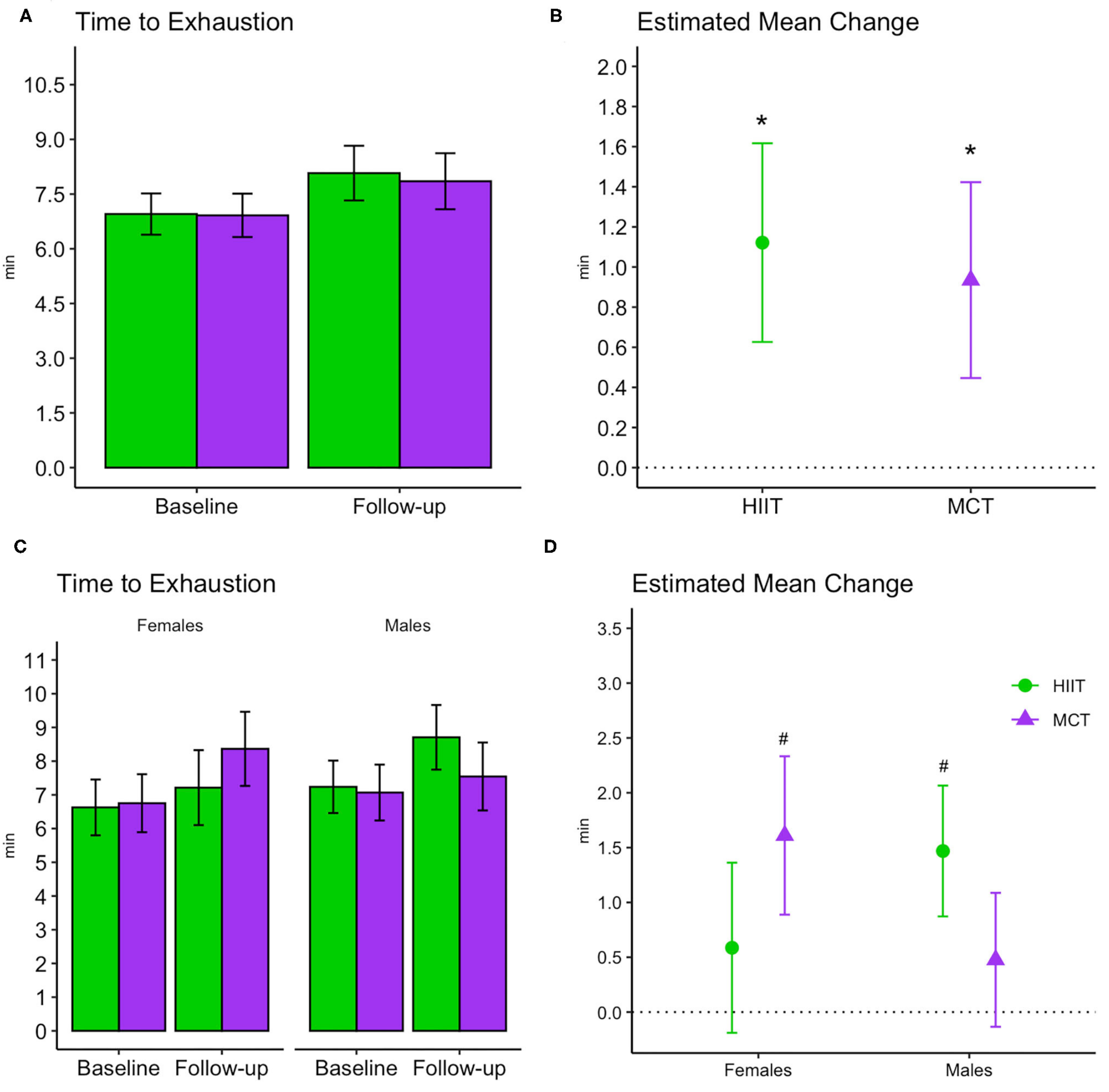

FIGURE 7 | Baseline and follow-up means for time to exhaustion during exercise stress tests (bar plots, group mean and 95% CI) and estimated mean change from baseline to 6 months (scatterplots, estimated mean change and 95% CI). **(A,B)** Display changes for the entire sample, while **(C,D)** display changes stratified by males and females. *, significant changes over time; #, significant subgroup changes over time at adjusted significance threshold ($p \leq 0.005$), with improvements in females within the MCT group [estimated mean change (95% CI): 1.61 min (0.9 to 2.33), $p = 0.00003$] and males within the HIIT group [1.47 min, (0.87 to 2.07), $p = 0.000006$]. See **Supplementary Table 3** for further details. HIIT, high-intensity interval training; MCT, moderate-intensity continuous training.

the greatest effect on participants with high BP at study entry compared to individuals with low BP across groups.

Despite lack of changes in SBP, we reported reduction in DBP following the program within the HIIT group. Noteworthy, 9 participants reported changes in their BP medication throughout the study. We repeated our analysis excluding these participants and DBP changes remained significant within the HIIT group, which may strengthen our results. These findings may hint at a specific positive impact of HIIT on DBP control in this population, similar to the results by Iellamo et al. (2014); however, this can be considered a small effect size and more conclusive evidence is warranted. As such, even though our findings and previous literature suggest HIIT could positively impact DBP to greater extent in hypertensive older adults, while also possibly improving SBP in those with uncontrolled BP (Molmen-Hansen et al., 2012; Iellamo et al., 2014), HIIT and MCT may in fact have similar effects in this population. Furthermore, the extent to which these potential improvements will reflect cognitive enhancements remains to be determined.

It is possible that the high attrition rate and low adherence to the exercise sessions may have hindered greater effects of our program. It is plausible that these shortcomings were a result of the demands of taking part in an exercise program centered at guaranteeing that participants complied with the exercise intensities prescribed. We used objective and subjective measures of exercise intensity, including immediate continuous feedback, to ensure compliance with the training protocols. These considerations, however, remain speculative and these shortcomings should be carefully considered in future exercise studies with this population.

LIMITATIONS

We included individuals with controlled and uncontrolled hypertension, and did not account for the effects of diet, smoking, alcohol intake and physical activity levels (Gottesman et al., 2017). Adjusting for these factors could have impacted study results, especially past physical activity levels and sedentary time—considering that these are modifiable risk factors for cardiovascular disease and have been shown to impact cognition across the life span (Falck et al., 2017). The usage of BP medication that decreases HR in this population also poses a challenge for accurately prescribing exercise intensity based on %HRmax—hence, RPE was also used to mitigate this issue in the current study. Furthermore, approximately 84% of participants achieved 80% or more of their age-predicted HRmax ($208 - 0.7 \times$ age) (Tanaka et al., 2001) at baseline, suggesting that any HR-lowering effect of BP medication did not have a substantial impact on our sample. We also noted a trend for differences between groups in history of depression (**Table 1**), with the MCT group including more patients with this condition. Adjusting for history of depression in the models showed that it had a significant contribution to models of cardiorespiratory fitness (all $p < 0.017$), however it did not change overall study results. Future studies should consider exploring this relationship of cardiorespiratory fitness improvements and depression in older adults with hypertension.

Also, although the CBS cognitive battery is grounded in well-validated neuropsychological tests (Hampshire et al., 2012), it has not been widely used in exercise studies and it may lack sensitivity in our clinical sample. That said, this seems unlikely, because the tasks have previously been shown to be highly sensitive to subtle cognitive differences related to disease or pharmacological intervention. For example, the test of planning (the Hampshire Tree Task) is sensitive to performance differences between specific genotypes in early Parkinson's disease (Williams-Gray et al., 2007); tests of paired-associates learning, such as the one employed in this study, are able to distinguish between first-episode schizophreniform psychosis and established schizophrenia (Wood et al., 2002) and the Token Search task used here has been used to detect increases in spatial working memory in children with attention deficit/hyperactivity disorder following a low dose of methylphenidate (Mehta et al., 2000).

We were unable to collect neuroimaging or biomarker data in this trial, and accordingly, this limits our ability to fully assess the impact of HIIT compared to MCT on underlying mechanisms for cognitive improvement. As well, another potential limitation is that we did not include a non-exercising control group in the current study. The lack of such control group poses a challenge to determine whether our results reflect the effects of extrinsic mechanisms, especially for cognition. Aerobic-based exercise does appear to have a positive effect on cognition compared to controls, and is already recommended as a non-pharmacological approach to mitigate dementia risk (Livingston et al., 2020; Yu et al., 2020). Meanwhile, our overarching goal was to determine whether exercising at higher intensity would be superior to a moderate intensity intervention. That is, modulating key elements of an intervention to further refine exercise prescription in clinical populations at risk of dementia, as we have done in the past (Gill et al., 2016; Gregory et al., 2017; Heath et al., 2017; Shellington et al., 2017; Boa Sorte Silva et al., 2018, 2020b). As such, the inclusion of non-exercising control group was not within the scope of the current study.

Lastly, participants were predominantly Caucasian, highly educated and functionally independent, limiting generalizability of our findings. Exercise sessions for the final wave of participants ended 3 weeks earlier due to closures caused by the COVID-19 pandemic, which also prevented 13 participants from attending their final assessment (impacting our attrition rate).

FUTURE DIRECTIONS

Future studies should emphasize comprehensive multidomain interventions for individuals with hypertension and SCD. This is relevant since pharmacological therapies to treat hypertension do not seem to reduce dementia risk (Williamson et al., 2019). Emerging evidence suggests synergistic effects on cognition and SBP as a result of exercise, a healthy diet and weight management in hypertensive middle-aged adults (Smith et al., 2010). Replicating these findings in older adults with SCD and hypertension could allow refinement of lifestyle interventions to reduce dementia risk.

CONCLUSIONS

In this trial involving community-dwelling older adults with history of hypertension and SCD, aerobic exercise of either high or moderate-intensity, combined with mind-motor training, did not improve cognition or SBP, despite improvements in cardiorespiratory fitness and lower-level cognitive functioning.

DATA AVAILABILITY STATEMENT

Data will be made available upon reasonable request. Requests to access the datasets should be directed to robert.petrella@ubc.ca.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Western University Health Sciences Research Ethics Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NB contributed to study concept and design, recruitment, implementation, data management, data analysis, interpretation of results, and drafted the manuscript. AP, CM, and NC contributed to recruitment, implementation, data management, interpretation of results, and critical review of the manuscript. DG contributed to study concept and design, data analysis, interpretation of results, and critical review of the manuscript. AO contributed to study design, interpretation of results, and critical review of the manuscript. RP contributed to study concept and design, recruitment, implementation, data management, data analysis, interpretation of results, critical review of the manuscript, and secured funding for the study. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.643809/full#supplementary-material

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Conflict of Interest: The cognitive tests used in this study are marketed by Cambridge Brain Sciences, of which AO is the Chief Scientific Officer. Under the terms of the existing licensing agreement, AO and his collaborators are free to use the platform at no cost for their scientific studies, and such research projects neither contribute to, nor are influenced by, the activities of the company. Consequently, there is no overlap between the current study and the activities of Cambridge Brain Sciences, nor was there any cost to the authors, funding bodies, or participants who were involved in the study.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Mind-Body Exercise Modulates Locus Coeruleus and Ventral Tegmental Area Functional Connectivity in Individuals With Mild Cognitive Impairment

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Mild cognitive impairment (MCI) is a common global health problem. Recently, the potential of mind-body intervention for MCI has drawn the interest of investigators. This study aims to comparatively explore the modulation effect of Baduanjin, a popular mind-body exercise, and physical exercise on the cognitive function, as well as the norepinephrine and dopamine systems using the resting state functional connectivity (rsFC) method in patients with MCI. 69 patients were randomized to the Baduanjin, brisk walking, or healthy education control group for 6 months. The Montreal Cognitive Assessment (MoCA) and magnetic resonance imaging (MRI) scans were applied at baseline and at the end of the experiment. Results showed that (1) compared to the brisk walking, the Baduanjin significantly increased MoCA scores; (2) Baduanjin significantly increased the right locus coeruleus (LC) and left ventral tegmental area (VTA) rsFC with the right insula and right amygdala compared to that of the control group; and the right anterior cingulate cortex (ACC) compared to that of the brisk walking group; (3) the increased right LC-right insula rsFC and right LC-right ACC rsFC were significantly associated with the corresponding MoCA score after 6-months of intervention; (4) both exercise groups experienced an increased effective connectivity from the right ACC to the left VTA compared to the control group; and (5) Baduanjin group experienced an increase in gray matter volume in the right ACC compared to the control group. Our results suggest that Baduanjin can significantly modulate intrinsic functional connectivity and the influence of the norepinephrine (LC) and dopamine (VTA) systems. These findings may shed light on the mechanisms of mind-body intervention and aid the development of new treatments for MCI.

Keywords: Baduanjin, resting state functional connectivity, mild cognitive impairment, locus coeruleus, ventral tegmental area

INTRODUCTION

Mild cognitive impairment (MCI) is a condition characterized by impaired cognitive function with a minimal impact on activities of daily living. Current pharmacologic treatments for the condition are unsatisfactory. Exercise has been recently recommended to improve cognitive function in patients with MCI (Petersen et al., 2018). Literature also suggests that mindful movement (mind-body intervention), which combines mindfulness and physical exercise, may have synergistic effects and lead to better outcomes than those achieved from either physical exercise or mindfulness meditation alone (Burgener et al., 2008).

Baduanjin is a mind-body exercise that focuses on both mindfulness and the strengthening of muscles and tendons (Liao et al., 2015). Previous studies have found that Baduanjin can improve attention, executive control function, and memory function, as well as modulate cognition-related brain function and structure. For instance, we found that compared to the education control, 12-week Baduanjin training significantly improved the memory quotient (MQ) and resting state functional connectivity of dorsal lateral prefrontal cortex (DLPFC) and hippocampus in elderly adults (Tao et al., 2016, 2017a). In another study in individuals with MCI, we found compared to the brisk walking and control groups, the Baduanjin can increased memory function as measured by Montreal Cognitive Assessment (MoCA), modulate the brain low-frequency oscillations, and increase gray matter volume of hippocampus and anterior cingulate cortex (ACC) (Tao et al., 2019).

More recently, a systematic review and meta-analysis of randomized controlled trials from 1054 participants showed that compared with conventional therapy, Baduanjin plus conventional therapy significantly improved cognitive and memory function in patients with mild cognitive impairment (Yu L. et al., 2020). In another pilot study, Xiao et al. (2020) found that community-delivered Baduanjin training program was safe for prefrail/frail older adults with the potential to improve cognitive function measured by MoCA.

Although accumulating evidence has demonstrated the potential of Baduanjin for cognition/memory improvement, its underlying mechanism remain unclear. Literature suggests that the release of stress-induced catecholamines may play an important role in cognitive processes (Zhang et al., 2016). Animal studies have found that the locus coeruleus (LC), a brain region involved in many cognitive processes, is a major node of norepinephrine (NE) release in the stress response (Liu et al., 2017). Takahashi et al. showed that compare to the healthy control, the LC contrast ratios significantly reduced in patient with Alzheimer's disease and mild cognitive impairment (Takahashi et al., 2014). Lee et al found that older adults were associated with decline in LC functional connectivity with frontoparietal networks that coordinate attentional selectivity (Lee et al., 2018).

Dopamine is another important catecholamine and a neurotransmitter involved in the reward and motivation process. Literature suggests that the ventral tegmental area (VTA), which projects to the nucleus accumbens and ACC (Navratilova et al., 2015), plays a crucial role in the release of dopamine (Lammel et al., 2014). Accumulating literature suggest that dopamine is involved in both dementia (Koch et al., 2020) and exercise (Fan et al., 2021). For instance, a previous study found that degeneration of VTA dopaminergic neurons at pre-plaque stages contributes to memory deficits and dysfunction of reward processing in dementia (Nobili et al., 2017).

Locus coeruleus-NE and VTA-dopamine systems have many similarities in physiological effects, and both are responsive to motivationally salient events (such as reward predictors) (Ranjbar-Slamloo and Fazlali, 2020). Disturbances of both have been implicated in highly overlapping sets of clinical disorders, such as attention deficit disorder (Unsworth and Robison, 2017) and Autism (Huang et al., 2021). The interaction of these two systems may plan an important role in pathophysiology of cognitive disorders such as MCI (Aston-Jones and Cohen, 2005).

In the present study, we comparatively investigated the modulation effects of 6 months of Baduanjin exercise, compared to brisk walking and a healthy education control, on resting state functional connectivity (rsFC) of key regions of the norepinephrine (LC) and dopamine (VTA) systems. In addition, we also applied exploratory effective connectivity analysis and region-of-interest-based gray matter volume (GMV) analysis in key regions derived from the LC and VTA rsFC analysis. We hypothesized that, compared to the brisk walking and healthy education control interventions, Baduanjin exercise would significantly modulate the LC and VTA resting state functional connectivity and effective connectivity within key regions of the two systems (amygdala, prefrontal cortex, hippocampus/parahippocampus for LC (Zhang et al., 2016; Jacobs et al., 2018)) and mesolimbic and mesocortical pathways such as the ACC, medial prefrontal cortex, and hippocampus for VTA (Zhang et al., 2016; Yu S. et al., 2020). Additionally, we hypothesize that the functional connectivity changes may be associated with the cognitive function improvement.

MATERIALS AND METHODS

The randomized controlled trial with three parallel groups (Baduanjin, brisk walking, and a healthy education control) was approved by the Medical Ethics Committee of the Second People's Hospital of Fujian Province (Fuzhou, China) and was registered in the Chinese Clinical Trial Registry (ChiCTR-ICR-15005795). All subjects gave their informed consent at the initiation of study procedures, and details of these procedures can be found in our previous publication (Tao et al., 2019) in which we investigate the modulation effect of Baduanjin using the Amplitude of low-frequency fluctuations (ALFF), region-of-interest voxel-based morphometry (VBM) Analysis, and rsFC of hippocampus and ACC (based on the ALFF results). In this study, we focused on

Abbreviations: MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; LC, locus coeruleus; VTA, ventral tegmental area; rsFC, resting state functional connectivity; ACC, anterior cingulate cortex; GMV, gray matter volume; VBM Voxel-Based Morphometry; TPJ, temporoparietal junction; DLPFC, dorsolateral prefrontal cortex.

the modulation effect of Baduanjin on the LC-NE and VTA-dopamine system, which has not been previously published. Approximately half of all subjects each group who enrolled in the clinical trial were randomly selected to undergo MRI/functional MRI brain scans ($n = 23$ each group). This manuscript focuses on the participants with MRI data.

Patients

Inclusion criteria included: 1. Aged 60 years or older; 2. No regular physical exercise for at least half a year (exercise with a frequency of at least twice a week and 20 min per session); 3. Having a physician's diagnosis of MCI based on the Petersen diagnostic criteria (Petersen, 2004); 4. Memory problems with MoCA score < 26 (if years of education ≤ 12, one point will be added to the patient's score); 5. Cognitive decline in accordance with age and education; 6. Intact activities of daily living (Lawton–Brody ADL score < 18); 7. Absence of dementia (Global Deterioration Scale score at 2 or 3).

Subjects were excluded from the study if any of the following criteria were met: 1. Resistant hypertension; 2. Severe vision or hearing loss; 3. Evidence of severe psychiatric conditions (such as active suicidal ideation, schizophrenia, etc.) or Geriatric depression scale score (GDS) ≥ 10 (Scale, 1997); 4. Current severe medical conditions for which exercise is contraindicated; 5. History of alcohol or drug abuse; 6. Participation in other clinical studies; 7. Pharmacologic treatments that may interfere with cognitive function.

Intervention

All participants in the study received health education every 8 weeks for 30 min per session. In these sessions, participants were educated on ways to prevent the development of MCI.

Participants in the Baduanjin and brisk walking groups received the 24-week exercise training with a frequency of 3 days/week, 60 min/day (15-min warm up, 40-min training, and 5-min cool down). Research staff members also participated in all training sessions to record the attendance of each subject.

Baduanjin training was based on the 'Health Qigong Baduanjin Standard,' which was enacted by the Chinese State Sports General Administration in Health Qigong Management Center of General Administration of Sport of China. (2003) and consists of 10 postures (including the preparation and ending posture) (Zheng et al., 2016). Two professional coaches with over 5 years of Baduanjin teaching experience at the Fujian University of Traditional Chinese Medicine were employed to guide participants' training.

In the brisk walking group, professional coaches were employed to guide participants' training. The intensity of the exercise was controlled by maintaining participants' heart rates at 55–75% of their heart rate reserve via the Polar Heart Rate Monitor.

Subjects in the healthy education control group were required to maintain their original physical activity levels and did not receive any specific exercise interventions except for the health education.

Behavioral Outcome

The Chinese version of the Montreal Cognitive Assessment (MoCA-Chinese Beijing version) scale was selected as our primary clinical outcome measure to assess global cognitive function. MoCA is a brief cognitive screening instrument that was created and validated to detect MCI (about 10-min). There are 8 items (visuospatial/executive functions, naming, verbal memory registration and learning, attention, abstraction, 5-min delayed verbal memory, and orientation) with a total score of 0-30 (a higher score equates to better function). The MoCA-Chinese Beijing version demonstrated an excellent sensitivity of 90.4% and a fair specificity (31.3%) when the cut-off score was recommended 26 (Yu et al., 2012; Zheng et al., 2016).The MoCA was measured at baseline and within one week after the 24-week intervention for all participants.

Functional and Structural MRI Data Acquisition

The fMRI data was acquired on a 3.0-T GE scanner (General Electric, Milwaukee, WI, United States) with an eight-channel phased array head coil at baseline and at the end of the intervention. Resting state functional MRI data was acquired with the following parameters: TR = 2100 ms, TE = 30 ms, flip angle = 90°, voxel size = 3.125 mm × 3.125 mm × 3.6 mm, 42 axial slices, field of view (FOV) = 200 mm × 200 mm, time pointes = 160. High-resolution structural images (MPRAGE) were acquired with the parameters of 7° flip angle, voxel size: $1 \times 1 \times 1$ mm^3, 240 mm FOV, and 164 slices. Subjects were asked to stay awake and remain motionless during the scan with their eyes closed and ears plugged.

Data Analysis and Statistics

Behavioral Data Analysis

One-way ANOVA and Chi-square tests were applied to compare the baseline characteristics of subjects, and ANCOVA was applied to compare changes (post-treatment minus pre-treatment) in MoCA scores across all groups, adjusted for age (years), gender, education, and baseline MoCA scores using IBM SPSS Statistics software (Dimitrov and Rumrill, 2003).

Seed-to-Voxel Functional Connectivity Correlational Analysis

Similar to our previous study (Liu et al., 2019a,c; Tao et al., 2019), the seed-to-voxel functional connectivity correlational analyses were performed using a standard pipeline in a functional connectivity toolbox (CONN[1]) in MATLAB. The seeds (regions of interest) of bilateral LC and VTA (left and right separately) used in the present study were applied based on previous studies. The left LC was defined as 4 × 6 × 10 mm centered at MNI coordinates −5,−34,−21, and the right LC was defined as 4 × 6 × 10 mm centered at MNI coordinates 7,−34,−21 (Naidich et al., 2009; Bär et al., 2016). The VTA was defined as a 4 mm radius sphere (MNI coordinates left VTA: −4,−15,−9; right VTA: 5,−14,−8) (Adcock et al., 2006). The images were

[1] http://www.nitrc.org/projects/conn

slice-time corrected, realigned, coregistered to subjects' respective structural images, normalized, and smoothed with a 4 mm full width half maximum (FWHM) kernel. Then, segmentation of gray matter, white matter, and cerebrospinal fluid (CSF) areas for the removal of temporal confounding factors was employed. Band-pass filtering was performed with a frequency window of 0.01 to 0.089 Hz.

To eliminate correlations caused by head motion and artifacts, we identified outlier time points in the motion parameters and global signal intensity using ART[2]. We treated images as outliers if the composite movement from a preceding image exceeded 0.5 mm or if the global mean intensity was greater than 3 standard deviations from the mean image intensity (Wang Z. et al., 2017). The temporal time series of the head motion matrix of outliers were put into the first-level analysis as covariates (Whitfield and Nieto, 2012). A threshold of $p < 0.005$ uncorrected in voxel level and $p < 0.05$ FDR corrected at cluster level was used for group analysis. Due to the important role of the amygdala in the modulation of emotion, stress, and mind-body intervention (Tang et al., 2015) and the small size of the area, we pre-defined the bilateral amygdala as a region of interest (ROI). For the ROI (as defined by AAL brain atlas), a threshold of voxel-wise $p < 0.005$ was used in data analysis. Monte Carlo simulations using the 3dFWHMx and 3dClustSim [AFNI[3] released in July 2017] were applied to correct for multiple comparisons (Gollub et al., 2018).

Exploratory Spectral Dynamic Causal Modeling Analysis

We found the overlapped brain regions in the right ACC and right insula among the rsFC of the right LC and left VTA (see results). To further investigate the causal interaction underlying the four brain regions (overlapped right ACC, overlapped right insula, ROIs of right LC and left VTA) during intervention, we performed the effective connectivity analysis using dynamic causal modeling (Sharaev et al., 2016; Li et al., 2017). The Spectral DCM analysis was performed using DCM12 (Wellcome Trust Centre for Neuroimaging, London, United Kingdom) implemented in SPM12. We specified two connectivity models: one model including the right LC, right ACC, and right insula (named the "right LC model"), and the other model including the left VTA, right ACC, and right insula (named the "left VTA model"). Four different sub-models were specified for each model: one fully connected model with bi-directional connections between all pairs of ROIs and three models where different regions predominantly affected the others (Sharaev et al., 2016; **Figures 3A1,B1**). In addition, to further investigate whether there were causal interactions between the left VTA and right LC, we defined a connectivity model that included all four brain masks (named the "right LC and left VTA model"). This model included five different sub-models: one fully connected model and four models where different regions predominantly affected the others (**Supplementary Figure 1A**). In this study, we assumed that all participants in the same conditions (i.e., pre-Baduanjin, post-Baduanjin, pre-walking, post-walking, pre-control, post-control) used the same model (the wining model).

Time series of the four brain masks of each subject (pre- and post-treatment separately) were extracted via a General Linear Model (GLM). The 6-rigid body realignment parameters (six head motion parameters) and the signals of cerebrospinal fluid and white matter were used as constant regresses in the GLM. Random Effects Bayesian model selection (RFX-BMS) was performed to determine the best model in each condition, considering both accuracy and complexity (Stephan et al., 2009). Repeated measures analysis was used to investigate the group and time interaction of the different connectivity parameters for the "wining" model.

Exploratory Region of Interest Voxel-Based Morphometry (VBM) Analysis

To investigate whether there were structural changes (gray matter volume, GMV) in the brain regions that showed significant group differences (Baduanjin vs. Control) and overlap between the rsFC of the right LC and left VTA (i.e., right amygdala, right ACC, and right insula; see Results for more information), we applied a region of interest VBM analysis (Andrew et al., 2018; Liu et al., 2019a,b; Tao et al., 2019) in SPM12. The data preprocessing for VBM analysis was similar to our previous study (Tao et al., 2017c). The T1 images of all participants were segmented into gray matter, white matter, and cerebrospinal fluid. Then, a group specific template was created after the images were normalized using the high dimensional DARTEL algorithm. Spatial smoothing was conducted with a 6 mm FWHM after the template was normalized into the standard Montreal Neurological Institute (MNI) space. A factorial design module with two factors (i.e., groups with three levels and time with two levels) was applied to explore the group differences. Age and gender were also included in the model as covariates. An absolute threshold of 0.1 was used for masking (Tao et al., 2017c). Total intracranial volume was obtained by summing up the overall volumes of gray matter, white matter, and cerebrospinal fluid. Then, we extracted the average GMV values of all voxels with the overlapping brain masks (i.e., right ACC, right amygdala, and right insula) in the three groups derived from functional connectivity analysis. ANCOVA was applied to compare changes of the three groups (post-treatment minus pre-treatment) with age and gender as covariates (Dimitrov and Rumrill, 2003).

RESULTS

Sixty-nine MCI patients completed the baseline behavioral test and MRI scan, and 57 subjects finished the study and were included in data analysis (Baduanjin group $n = 20$, brisk walking group $n = 17$, and health education control group $n = 20$). Three subjects dropped out of the Baduanjin group (one subject withdrew voluntarily, and two were unwilling to participate in the second MRI scan). Six subjects dropped out of the brisk walking group (one withdrew voluntarily, one was unwilling to participate in the second MoCA test, one was lost to follow-up, and three had poor-quality MRI data). Three subjects dropped

[2] https://www.nitrc.org/projects/artifact_detect

[3] https://afni.nimh.nih.gov

out of the control group (one was lost to follow-up, and two were unwilling to participate in the second MoCA test). No subject reported taking additional pharmacological treatment during the training. The attendance rates (mean ± SD) for the Baduanjin and brisk walking groups were 0.842 ± 0.100 and 0.838 ± 0.116, respectively, and there were no significant differences between the two exercise groups in terms of attendance rate ($p = 0.927$).

Behavioral Results

Baseline characteristics and MoCA scores of participants are listed in **Table 1**. There were no significant differences in age, gender, education, score on the Geriatric depression scale (GDS), or MoCA scores among the three groups at baseline (three-group comparison *p*-Value as follows: Age: $p = 0.395$; Gender: $p = 0.563$; Education: $p = 0.675$; GDS: $p = 0.12$; pre-MoCA: $p = 0.141$).

ANCOVA showed a significant difference in MoCA score changes (post-treatment minus pre-treatment) among the three groups ($F_{2,50} = 4.311$; $p = 0.019$). *Post hoc* analysis showed that the Baduanjin group had a significant increase in MoCA scores compared to the health education control group ($p = 0.05$) and the brisk walking group ($p = 0.037$) after Sidak correction. There was no significant difference between the brisk walking group and the control group ($p = 0.989$, **Table 1**).

Seed-to-Voxel rsFC Results

In present study, we used T2 imaging data to check whether the participants have underlying brain diseases, such as brain tumors or lesions. No obvious brain abnormalities were detected. No subject was excluded due to the head movement in the study.

Seed-to-Voxel rsFC Analysis Using the LC as the Seed

Seed-to-voxel rsFC analysis using the left LC as the seed showed increased rsFC in the bilateral temporoparietal junction (TPJ), right insula, inferior frontal gyrus, supplemental motor area, and postcentral gyrus in the Baduanjin group compared to the control group. The analysis also showed increased rsFC in the right dorsolateral prefrontal cortex and decreased rsFC in the bilateral cerebellum exterior in the Baduanjin group compared to the brisk walking group. There was no other significant group difference at the threshold we set (**Figures 1A1,A2,B** and **Table 2**).

Seed-to-voxel rsFC analysis using the right LC as the seed showed that Baduanjin group is associated with increased rsFC in the bilateral ACC, bilateral precentral gyrus, right insula, amygdala, TPJ, supplemental motor area, and superior temporal gyrus compared to the control group, as well as increased rsFC in the right ACC compared to the brisk walking group. Compared to the Baduanjin group, there was significantly increased rsFC in the right supplemental motor cortex, inferior occipital cortex, bilateral precentral & postcentral cortex, left middle occipital cortex, and right cerebellum in the brisk walking group. There was no other significant group difference at the threshold we set (**Figures 1C1,C2,D** and **Table 2**).

Interestingly, we found an overlapping increased right LC-right ACC rsFC in the Baduanjin group compared to the control and brisk walking groups. We also found that both the left and right LC are associated with increased rsFC with the right insula in the Baduanjin group compared to the control group. We extracted the average *z*-Values of the two rsFCs associated with the right LC (rsFC of right ACC-right LC and rsFC of right insula-right LC) in the three groups after treatment and performed a multiple regression analysis including age and gender as covariates. We found a significant positive association between rsFC *z*-Values at the right ACC and right insula (right ACC: $r = 0.265$, $p = 0.046$; right insula: $r = 0.277$, $p = 0.037$) and corresponding MoCA scores after FDR correlation across all subjects in three groups.

Seed-to-Voxel rsFC Analysis Using the VTA as the Seed

Seed-to-voxel analysis using the left VTA as the seed showed significantly increased rsFC in the bilateral anterior insula, putamen, caudate; right amygdala, orbital frontal gyrus, postcentral gyrus; and left nucleus accumbent and superior parietal gyrus in the Baduanjin group compared to the control group. Analysis also showed significantly decreased rsFC in the left posterior cingulate cortex in the Baduanjin group compared to the control group and increased rsFC in the bilateral ACC compared to the brisk walking group. We also found significantly decreased rsFC in the left precuneus in the brisk walking group compared to the control group. We did not find any other significant group differences above the threshold we set (**Table 2**).

Seed-to-voxel analysis using the right VTA as the seed showed an increased rsFC in the right TPJ in the Baduanjin group compared to the brisk walking group. There was also a decreased

TABLE 1 | Demographics of study participants and clinical outcome results.

	Baduanjin ($n = 20$)	Walking ($n = 17$)	Control ($n = 20$)	*F* or Chi-square value	*P*-value
Age†(mean(SD))	66.17(4.17)	64.32(2.60)	65.97(5.66)	0.945	0.395
Gender‡(male/female)	5/15	7/10	6/14	1.148	0.563
Education‡ (1/2/3/4)	3/6/6/5	2/5/9/1	3/4/8/5	4.016	0.675
Geriatric depression scale (GDS) †(mean(SD))	6.05(2.84)	4.18(2.65)	5.50(2.76)	2.204	0.120
Pre-MoCA†(mean(SD))	22.45(2.16)	21.47(2.27)	21.00(2.36)	2.035	0.141
MoCA change (mean(SD))	2.10(2.25)	0.88(1.96)	1.10(1.48)	4.311	0.019

†p-Values were calculated with one-way analysis of variance, ‡p-Values were calculated with a chi-square test. Education 1: primary school; 2: middle school; 3: high school; 4: college and above. Baduanjin: Baduanjin group; Walking: brisk walking group; Control: non-exercise group; MoCA change: post-treatment MoCA score minus pre-treatment MoCA.

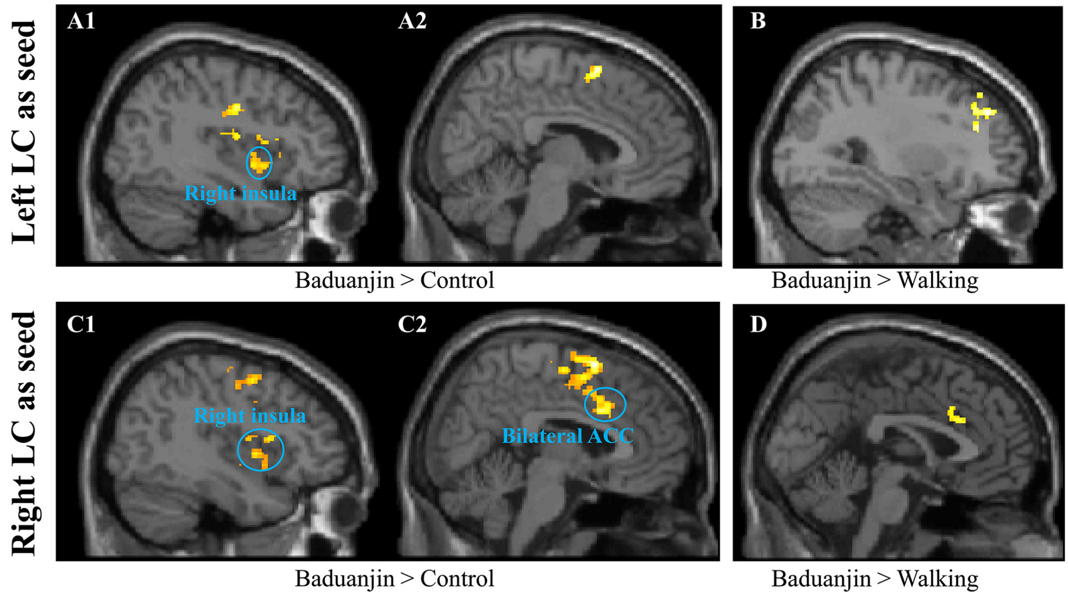

FIGURE 1 | Resting state functional connectivity results using the LC as the seed. **(A1,A2,B)**: using the left LC as the seed. **(A1,A2)**, Baduanjin > Control; **(B)** Baduanjin > Brisk Walking. **(C1,C2,D)**, using the right LC as the seed. **(C1,C2)**, Baduanjin > Control; **(D)** Baduanjin > Brisk Walking.

rsFC in the bilateral precuneus in the brisk walking group compared to the control group. No other significant group difference was found at the threshold we set (**Table 2**).

We found that both the right LC and left VTA are associated with increased rsFC with the right insula and right amygdala in the Baduanjin group as compared to the control group (the rsFCs of right insula-right LC/left VTA; the rsFCs of right amygdala-right LC/left VTA). We also found an overlapping brain region in the right ACC in the two rsFCs analyses (i.e., the rsFC of right LC-right ACC and the rsFC of left VTA-bilateral ACC) in the Baduanijn group compared to the brisk walking group (**Figures 2A-C**).

Spectral Dynamic Causal Modeling Results

Random Effects Bayesian model analysis showed that the fully connected model was the best model at each condition (i.e., pre-Baduanjin, post-Baduanjin, pre-walking, post-walking, pre-control, post-control) in the "right LC model," "left VTA model" (**Figures 3A,B**), and "right LC and left VTA model" (**Supplementary Figure 1B**, see the **Supplementary Materials** for details).

We then performed the repeated measures analysis in each pair of endogenous connectivity (DCM.Ep.A) of the full model. No significant group and time interaction was found in the "right LC model" and "right LC and left VTA" model in all effective connectivity (see **Table 3** and **Supplementary Tables 1, 2**; for the right LC model, the group*time interaction *P*-value).

We found increased effective connectivity from the right ACC to the left VTA in the Baduanjin and brisk walking groups and decreased effective connectivity in the control group after intervention, with significant group and time interactions (p = 0.041) in the "left VTA model." No other significant effective connectivity group and time interaction was found in the "left VTA model" (**Figures 3C1, C2**, **Table 3**, and **Supplementary Table 1**).

Region of Interest Voxel-Based Morphometry (VBM) Analysis

We compared VBM changes (post-treatment minus pre-treatment) at the right ACC, right insula, and right amygdala after different treatments and found a significant group difference in right ACC GMV ($F_{2,50}$ = 14.076; p < 0.001). *Post hoc* analysis revealed increased GMV in the right ACC of the Baduanjin group compared to the control group (p < 0.001) and brisk walking group (p < 0.001), but no significant group difference between the brisk walking and control groups (p = 0.621) after Sidak correction (**Figure 2D**). No significant GMV difference was found in the right insula and right amygdala among groups (p > 0.05).

DISCUSSION

In the present study, we investigated the modulation effects of 6 months of Baduanjin on LC and VTA system in patients with MCI. We found that Baduanjin can significantly modulate the rsFC of the LC and VTA and increase gray matter volume of the right ACC compared to brisk walking and health education. In addition, we found a significant group and time interaction in the effective connectivity from right ACC to left VTA. Our results support our research hypothesis that Baduanjin can modulate intrinsic functional connectivity of norepinephrine (LC) and dopamine (VTA) systems.

TABLE 2 | Resting state functional connectivity results using LC and VTA as seeds.

Seed	Contrast	Cluster	*T*-value	*Z*-value	MNI coordinate			Brain region
					x	y	z	
Left LC	Baduanjin > Control	285	4.39	3.90	52	0	6	R insula
		113	4.61	4.06	52	−32	16	R TPJ
		130	3.94	3.57	−26	−36	40	L TPJ
		128	5.31	4.53	34	24	8	R inferior frontal
		135	5.29	4.52	8	12	66	R supplemental motor area
		120	4.37	3.89	48	14	14	R inferior frontal
		180	4.31	3.84	40	−8	36	R postcentral gyrus
	Control > Baduanjin	No brain region above threshold						
	Baduanjin > Walking	127	4.26	3.78	32	36	26	R DLPFC
	Walking > Baduanjin	152	4.34	3.83	−2	−62	−46	Bilateral Cerebellum exterior
	Walking > Control	No brain region above threshold						
	Control > Walking	No brain region above threshold						
Right LC	Baduanjin > Control	294	4.58	4.04	38	10	12	R insula
		21	3.58	3.29	20	4	−30	R amygdala
		198	4.82	4.2	52	−38	18	R TPJ
		643	5.81	4.85	4	8	64	R supplemental motor area
			3.77	3.44	6	12	38	Bilateral ACC
		423	5.24	4.48	−62	−2	6	L precentral gyrus
		107	4.86	4.23	24	−26	68	R precentral gyrus
		119	4.08	3.678	62	4	−2	R superior temporal gyrus
		345	4.59	4.05	44	2	54	R precentral gyrus
	Control > Baduanjin	No brain region above threshold						
	Baduanjin > Walking	125	4.63	4.04	6	14	32	Right ACC
	Walking > Baduanjin	96	5.86	4.82	4	−8	60	R supplement motor cortex
		91	4.82	4.17	42	−80	2	R inferior occipital cortex
		94	3.04	2.83	32	−22	60	R precentral cortex
		95	3.03	2.83	−60	−10	34	L postcentral cortex
		91	4.44	3.90	−30	−30	56	L precentral cortex
		189	4.08	3.64	58	−6	22	R pre & postcentral cortex
		99	4.04	3.62	−28	−94	14	L middle occipital cortex
		116	6.23	5.03	38	−60	−56	R cerebellum
	Walking > Control	No brain region above threshold						
	Control > Walking	No brain region above threshold						
Left VTA	Baduanjin > Control	527	3.77	3.43	40	2	2	R anterior insula
			3.50	3.22	20	2	−30	R amygdala
			5.20	4.46	22	12	0	R putamen
			5.15	4.43	−16	14	−2	L putamen/caudate
			4.24	3.80	22	16	−24	R orbital frontal gyrus
			4.14	3.72	10	14	0	R caudate
			3.99	3.61	−8	8	−8	L nucleus accumbent
		107	4.70	4.12	−28	24	2	L anterior insula
		186	4.97	4.31	54	−6	30	R postcentral gyrus
		107	4.05	3.65	−26	−56	56	L superior parietal gyrus
	Control > Baduanjin	130	5.00	4.33	−20	−54	22	L PCC
	Baduanjin > Walking	173	5.27	4.46	2	−4	36	Bilateral ACC
	Walking > Baduanjin	No brain region above threshold						
	Walking > Control	No brain region above threshold						
	Control > Walking	126	4.69	4.08	−4	−60	56	L precuneus
Right VTA	Baduanjin > Control	No brain region above threshold						
	Control > Baduanjin	No brain region above threshold						
	Baduanjin > Walking	154	6.59	5.23	28	−42	44	R TPJ
	Walking > Baduanjin	No brain region above threshold						
	Walking > Control	No brain region above threshold						
	Control > Walking	278	4.36	3.85	−4	−56	60	Bilateral precuneus

ACC: anterior cingulate cortex; PCC: posterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; TPJ: temporoparietal joint; L: left; R: right.

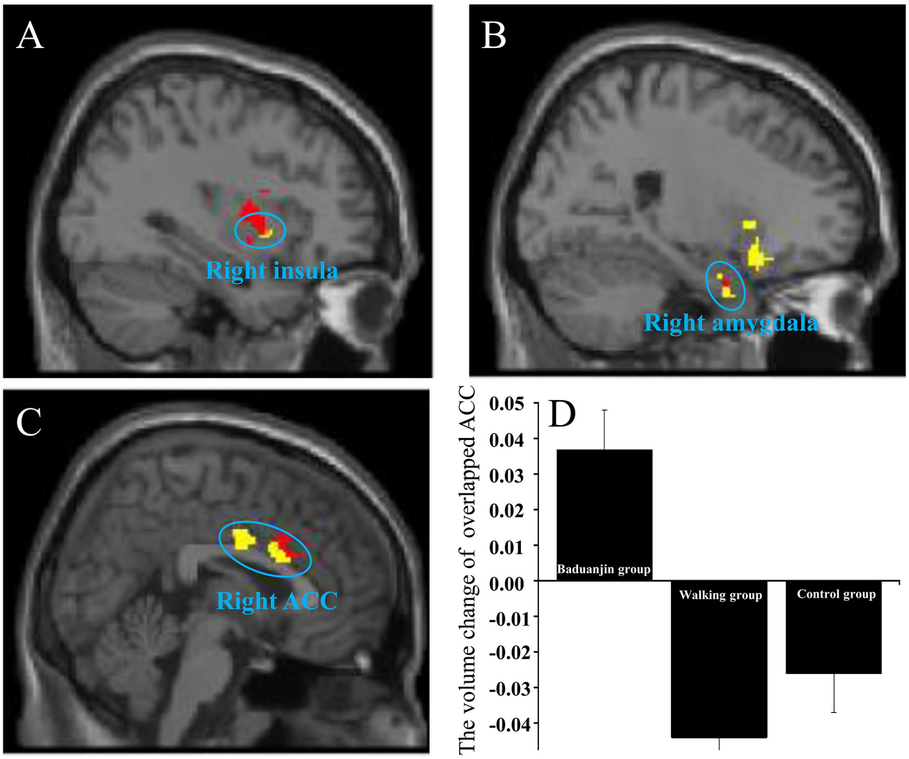

FIGURE 2 | The increased overlapping rsFC in the Baduanjin group between the right LC and left VTA compared to the control group/walking group and the VBM analysis of the overlapping brain region. **(A)** the overlapping brain region in the right insula; **(B)** the overlapping brain region in the right amygdala; **(C)** the overlapping brain region in the right ACC; Red, using the right LC as the seed; yellow, using the left VTA as the seed; **(D)** the ROI VBM analysis in the right ACC among the three groups.

Our findings that Baduanjin can significantly improve the cognitive function in patients with MCI are consistent with findings from a previous study that endorsed the treatment effects of mind-body exercise on MCI (Sungkarat et al., 2018), as well as our previous studies demonstrating that Baduanjin can prevent memory decline in healthy elders (Tao et al., 2017a,b,c). Interestingly, we did not find significant cognitive function improvement in the brisk walking group compared to the health education group. Some studies have suggested a positive effect of physical exercise on improving cognitive function or preventing cognitive decline (Baker et al., 2010; Brasure et al., 2018). However, a recent clinical study showed that intense aerobic exercise and strength exercise training resulted in no significant group differences in slowing cognitive impairment in people with mild to moderate dementia (Sarah et al., 2018). Further studies are needed to confirm our results.

We found that, compared to the brisk walking group, Baduanijn exercise significantly increased the rsFC between the right ACC and left VTA/right LC. The gray matter volume of the right ACC was significantly increased after 6 months of Baduanjin exercise compared to the brisk walking and health education groups. These findings are consistent with previous studies indicating the role of the ACC in cognition as well as a previous study based on the same data set in which we found increased amplitude of low-frequency fluctuations values (a measurement of brain low-frequency oscillations) in the bilateral ACC in the Baduanjin group compared to the control group (Tao et al., 2019).

Previous studies have found that ACC activation is involved in a number of cognitive processes, including decision making, model updating, and outcome-related activity (Kolling et al., 2016). Animal studies have suggested that the ACC provides prominent direct input to the LC, and that the connectivity between the LC and ACC is involved in cognitive processes like reinforcement learning (Aston-Jones and Cohen, 2005). The ACC may also be able to exert direct top-down control over the VTA (Thomas and David, 2017; Wang S. et al., 2017).

A previous study found that LC-NE and VTA-dopamine systems may interact synergistically to implement an auto-annealing reinforcement learning mechanism (Aston-Jones and Cohen, 2005). This finding aligns with our results, which showed overlapping rsFC in the ACC between the left LC and right VTA. Our results suggest that the ACC may play an important role in Baduanjin modulation by linking LC-NE and VTA-dopamine systems.

In addition, we found that the exercise groups had an increased effective connectivity from the right ACC to the left VTA and a marginally significant increase from the right ACC to the right LC (p = 0.066) compared to the control group (**Table 3** and **Supplementary Table 1**). Effective connectivity

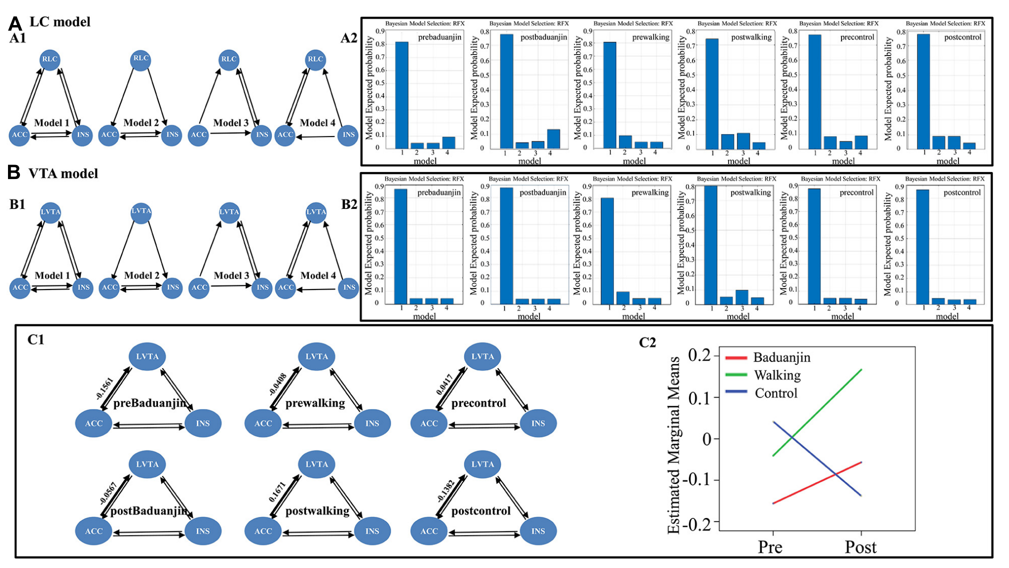

FIGURE 3 | The "right LC model" and "left VTA model" setup, the winning sub-model at the condition level in the "right LC model" and "left VTA model," and the group and time interaction of right ACC to left VTA effective connectivity. **(A)** The "right LC model" and the winning sub-model at the condition level in the "right LC model". **(A1)** right LC model setup: model 1-4, sub-model of the "right LC model," model 1-full connective model, model 2- right LC predominantly affected the others, model 3- right ACC predominantly affected the others, model 4-right insula predominantly affected the others; **(A2)** the winning sub-model of the "right LC model" in each condition (i.e., pre-Baduanjin, post-Baduanjin, pre-walking, post-walking, pre-control, post-control); **(B)** The "left VTA model" and the winning sub-model at the condition level in the "left VTA model". **(B1)** Left VTA model setup: model 1-4, sub-model of "left VTA model," model 1-full connective model, model 2-left VTA predominantly affected the others, model 3-rigth ACC predominantly affected the others, model 4-right insula predominantly affected the others; **(B2)** the winning sub-model of the "left VTA model" in each condition (i.e., pre-Baduanjin, post-Baduanjin, pre-walking, post-walking, pre-control, post-control). **(C)** Mean connection strengths and the group and time interaction of right ACC to left VTA effective connectivity. **(C1)** Mean connection strengths for the effective connectivity of right ACC to left VTA. **(C2)** The group and time interaction for the effective connectivity of right ACC to left VTA. RLC: right locus coeruleus; LVTA: left ventral tegmental area; ACC: right overlapped anterior cingulate cortex; INS: right overlapped insula.

analysis using DCM (Friston et al., 2003) can describe the causal relationships between brain regions in the functional MRI data (Friston and Penny, 2011; Sharaev et al., 2016).

TABLE 3 | The group and time interaction in the effective connectivity.

Effective connectivity	Time main effect *P*-value	Time*Group interaction *P*-value
Right LC model		
LC→ACC	0.050	0.334
LC→INS	0.817	0.732
ACC→LC	0.881	0.066
ACC→INS	0.246	0.515
INS→LC	0.455	0.588
INS→ACC	0.071	0.341
Left VTA model		
VTA→ACC	0.669	0.444
VTA→INS	0.913	0.404
ACC→VTA	0.502	0.041
ACC→INS	0.518	0.819
INS→VTA	0.084	0.291
INS→ACC	0.630	0.880

LC: ROI of right locus coeruleus; VTA: ROI of left ventral tegmental area; ACC: right overlapped anterior cingulate cortex; INS: right overlapped insula.

Specifically, effective connectivity can measure the influence that one neuronal system/brain region exerts on another (Sharaev et al., 2016). Recently, the method has been applied to investigate the modulation effect of mind-body intervention (Kong et al., 2021). Previous studies have suggested that the ACC has reciprocal anatomical connections with both the LC and VTA (Leichnetz and Astruc, 1976; Carmichael and Price, 1995). We found that the ACC has an increased causal influence on the VTA and LC (marginal significant) after exercise. This suggests that the ACC may play a major role in the modulation effect of exercise in patients with MCI.

The insula is a key member of the salience network and plays a role in regulating mental allocation (Ullsperger et al., 2010). Previous studies have suggested that anatomical connection between the LC and anterior insula may be associated with the processing of unexpected events (Dayan and Yu, 2006; Ullsperger et al., 2010). Hämmerer et al. (2018) found that older adults perform worse in a salient stimulation memory task than young adults. In addition, the insula is a dopaminergic region that functions to process stimulus salience and motivation, integrating information about task salience and regulating VTA excitability in response to reward (Rigoli et al., 2016). The above evidence suggests that the regulatory effect of the insula in cognitive function (especially in memory processing) of elders may be associated with the VTA and LC. In addition, studies have suggested that the structure and function of the insula can be significantly modulated by mindfulness training (Hodie lzel et al., 2008; Ives-Deliperi et al., 2011). We speculate that the increased rsFC between the VTA/LC and insula after Baduanjin training may represent the potential modulation of interoceptive awareness skills and salience event processing.

We also found an overlapping increased rsFC in the amygdala between the VTA and LC after Baduanjin exercise. Literature suggests that the amygdala plays a key role in the interaction of emotion and cognition (Phelps, 2006) and has a direct anatomical connection with the VTA-dopaminergic system (Thomas et al., 2018) and LC-noradrenergic system (Mohammed et al., 2016). A series of studies has suggested that stress affects the structure of the amygdala (Mitra et al., 2005; McEwen et al., 2016). Thus, Baduanjin may relieve stress and negative emotion (a key risk factor for the development of MCI) by modulating the interaction between the LC and VTA in the amygdala and further improving cognitive function.

We found increased rsFC of the LC-TPJ and VTA-TPJ in the Baduanjin group compared to both the control group and brisk walking group. The TPJ plays a key role in memory processing and social cognition (Carter and Huettel, 2013). Both the LC and TPJ are involved in executive and attentional processes (Laureiro-Martínez et al., 2015), and the functional connectivity between the TPJ and reward-related regions (such as the VTA) is involved in episodic encoding (Sugimoto et al., 2016). These results indicate that the TPJ may also be involved in the modulation effect of Baduanjin in cognition.

There are several limitations to our study. First, we did not evaluate levels of norepinephrine and dopamine directly. Further studies are needed to assess these neurotransmitter levels with neuroimaging techniques. Additionally, our sample size in this study was relatively small. Studies with larger sample sizes should be conducted to confirm our findings. Finally, we only measured global cognitive function via MoCA, and further research should be conducted to explore the treatment effects of Baduanjin on cognitive functions like memory and attention in patients with MCI.

CONCLUSION

In summary, we found that 6 months of Baduanjin exercise can significantly improve cognitive function compared to brisk walking and health education. In addition, Baduanjin can yield increases in LC and VTA rsFC with the ACC, insula, amygdala, and TPJ, increases in the effective connection of the ACC to LC/VTA, and increases in the gray matter volume of the ACC. Our findings suggest that Baduanjin may improve cognitive function in patients with MCI by modulating brain function and structure associated with the norepinephrine (LC) and dopamine (VTA) systems.

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 Medical Ethics Committee of the Second People's Hospital of Fujian Province. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

GZ and LC designed the experimental. RX, ML, MH, and SL contributed to the data collection. JL, JK, and JT contributed to the data analysis. JL, JK, JT, XC, GW, and JP prepared the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.646807/full#supplementary-material

Supplementary Figure 1 | The "right LC and left VTA model" setup and the winning sub-model at the condition level in the "right LC and left VTA model." **(A)** model 1-5, sub-model of the "right LC and left VTA model," model 1-full connective model, model 2-left VTA predominantly affected the others, model 3-right ACC predominantly affected the others, model 4-right insula predominantly affected the others; model 5-right LC predominantly affected the others; **(B)** the winning sub-model at the condition level in the "right LC and left VTA model." RLC: right locus coeruleus; LVTA: left ventral tegmental area; ACC: right overlapped anterior cingulate cortex; INS: right overlapped insula.

Supplementary Figure 2 | The number of subjects in each condition in each sub-model in the "right LC model," "left VTA model," and "right LC and left VTA model."

Supplementary Table 1 | Mean and Standard deviations of connection strengths.

Supplementary Table 2 | The group and time interaction in the effective connectivity ("right LC and left VTA" model).

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Conflict of Interest: JK has a disclosure to report (holding equity in a MNT, and pending patents to develop a new brain stimulation device).

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
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Benefits of Higher Cardiovascular and Motor Coordinative Fitness on Driving Behavior Are Mediated by Cognitive Functioning: A Path Analysis

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Driving is an important skill for older adults to maintain an independent lifestyle, and to preserve the quality of life. However, the ability to drive safely in older adults can be compromised by age-related cognitive decline. Performing an additional task during driving (e.g., adjusting the radio) increases cognitive demands and thus might additionally impair driving performance. Cognitive functioning has been shown to be positively related to physical activity/fitness such as cardiovascular and motor coordinative fitness. As such, a higher fitness level might be associated with higher cognitive resources and may therefore benefit driving performance under dual-task conditions. For the first time, the present study investigated whether this association of physical fitness and cognitive functioning causes an indirect relationship between physical fitness and dual-task driving performance through cognitive functions. Data from 120 healthy older adults (age: 69.56 ± 3.62, 53 female) were analyzed. Participants completed tests on cardiovascular fitness (cardiorespiratory capacity), motor coordinative fitness (composite score: static balance, psychomotor speed, bimanual dexterity), and cognitive functions (updating, inhibition, shifting, cognitive processing speed). Further, they performed a virtual car driving scenario where they additionally engaged in cognitively demanding tasks that were modeled after typical real-life activities during driving (typing or reasoning). Structural equation modeling (path analysis) was used to investigate whether cardiovascular and motor coordinative fitness were indirectly associated with lane keeping (i.e., variability in lateral position) and speed control (i.e., average velocity) while dual-task driving *via* cognitive functions. Both cardiovascular and motor coordinative fitness demonstrated the hypothesized indirect effects on dual-task driving. Motor coordinative fitness showed a significant indirect effect on lane keeping, while cardiovascular fitness demonstrated a trend-level indirect effect on speed control. Moreover, both fitness domains were positively related to different cognitive functions (processing speed and/or updating), and cognitive functions (updating or inhibition), in turn, were related to dual-task driving. These findings indicate that cognitive

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benefits associated with higher fitness may facilitate driving performance. Given that driving with lower cognitive capacity can result in serious consequences, this study emphasizes the importance for older adults to engage in a physically active lifestyle as it might serve as a preventive measure for driving safety.

Keywords: aging, car driving, dual-tasking, multitasking, executive functions, fitness, virtual reality, ecological validity

INTRODUCTION

Driving a car is an essential skill for older adults to preserve mobility and independent living (Owsley, 2002; Musselwhite et al., 2015). It has been suggested previously (Anstey et al., 2005; Karthaus and Falkenstein, 2016) that controlling a vehicle affords an effective integration of multiple perceptual (e.g., visual information), motor (e.g., upper and lower limb control), and cognitive functions (e.g., visuospatial skill, attention, cognitive processing speed). Those functions usually decline with higher age (Schaie and Willis, 2010; Seidler et al., 2010; Roberts and Allen, 2016; Anderson and Craik, 2017). As a result, car driving becomes increasingly cognitively demanding for older adults (Karthaus and Falkenstein, 2016). Cognitive demand during driving further increases when an additional task is performed concomitantly (i.e., dual- or multitasking), such as when adjusting the radio or talking to passengers (Vernon et al., 2015; Young et al., 2017; Depestele et al., 2020). In these complex, cognitively demanding situations, older adults are particularly at risk for accidents (Owsley et al., 1991; Aschersleben and Müsseler, 2008; Bélanger et al., 2010, 2015; Klauer et al., 2014; Dingus et al., 2016; Lombardi et al., 2017) as they seem to have difficulties in distributing their cognitive resources to both tasks simultaneously (Verhaeghen et al., 2003; Brustio et al., 2017). A higher level of cognitive functioning in older adults has been shown to be positively associated with their physical fitness level, both cardiovascular fitness and motor coordinative fitness (Voelcker-Rehage et al., 2010; Voelcker-Rehage and Niemann, 2013; Freudenberger et al., 2016). Hence being physically active/fit might not only preserve cognitive functioning but also driving performance, particularly under cognitively demanding conditions. No study, however, has yet investigated whether driving in the presence of an additional cognitive demand, as it is typically the case in daily life situations, indirectly benefits from higher physical fitness through higher cognitive functioning. Here, we address this issue using structural equation modeling (path analysis).

Age-related cognitive decline affects several cognitive functions that are associated with driving behavior such as attention, visuospatial skill, memory, or cognitive processing speed (Verhaeghen et al., 2003; Apolinario et al., 2009; Gajewski and Falkenstein, 2011; Wasylyshyn et al., 2011; Young and Bunce, 2011; Harada et al., 2013; Murman, 2015; Fraade-Blanar et al., 2018; Salthouse, 2019). For example, both visuospatial skill and attention are required to continuously monitor the environment while being able to very quickly identifying potential hazards on the road (Andrews and Westerman, 2012; Michaels et al., 2017; Eudave et al., 2018; Ledger et al., 2019). Many studies have demonstrated such positive associations between different cognitive functions and driving behavior in a variety of scenarios (e.g., car following, braking, overtaking), and for different performance parameters (e.g., lane keeping, speed control, braking reactions; Young and Bunce, 2011; Anstey et al., 2012; Depestele et al., 2020). Interestingly, the involvement of cognitive functions during driving seems to be more pronounced in older than in younger adults (Anstey et al., 2005; Lees et al., 2010; Fraade-Blanar et al., 2018), even though older adults are usually more experienced drivers and might preserve a relatively high level of automatization in driving (McKenna and Farrand, 1999; Lees et al., 2010; Charlton and Starkey, 2011; Anstey et al., 2012). When engaging in more complex or unexpected and hazardous situations, fluid cognitive functions such as inhibition, updating, shifting, and cognitive processing speed seem to be required in particular, and especially in older persons (Young and Bunce, 2011; Karthaus and Falkenstein, 2016). The former three functions (inhibition, updating, shifting) are often summarized under the umbrella term "executive functions" (see Miyake et al., 2000; Miyake and Friedman, 2012; Bock et al., 2019b). More recently, these functions have been discussed to play an important role in driving and accident risk among older adults, and particularly when simultaneously being involved in a cognitively demanding task (Mathias and Lucas, 2009; Asimakopulos et al., 2012; Harada et al., 2013; Karthaus and Falkenstein, 2016; Eramudugolla et al., 2017; Walshe et al., 2017; Haeger et al., 2018). For example, *inhibiting non-relevant or distracting information* during car driving is essential to keep attention focused on the road. In addition, when engaging in an additional task during driving (e.g., adjusting the radio) the driver is required to efficiently *shift* attention *between tasks* while also *holding and updating relevant environmental cues in mind* (Marmeleira et al., 2009; Karthaus and Falkenstein, 2016; Pope et al., 2017). Further, *cognitive processing speed* has been associated with driving behavior (Salthouse, 1996, 2009; Roenker et al., 2003; Edwards et al., 2009; Albinet et al., 2012; Eramudugolla et al., 2017), as it is important during complex cognitive-motor behaviors such as high traffic loads or driving while performing an additional task (Edwards et al., 2009; Künstler et al., 2018; Andersson and Peters, 2020). However, the cognitive mechanisms specifically involved in dual-task driving need to be further investigated as most studies on the relationship between cognitive functions and driving have been conducted in single-task settings (Depestele et al., 2020).

The level of cognitive functioning in older adults seems to be influenced by several lifestyle factors (Reuter-Lorenz and Park, 2014). In particular physical activity/fitness, such as cardiovascular and motor coordinative fitness, are positively related to cognitive functioning (Voelcker-Rehage and Niemann, 2013; Levin et al., 2017; Cabeza et al., 2018; Nystoriak and Bhatnagar, 2018; James et al., 2019). A large body of cross-sectional and longitudinal studies demonstrates this relationship (Voelcker-Rehage et al., 2010; Bherer et al., 2013; Diamond, 2013; Bherer, 2015; Dupuy et al., 2015; Young et al., 2015; Gajewski and Falkenstein, 2016; Gheysen et al., 2018; Diamond and Ling, 2019; Hillman et al., 2019; Ludyga et al., 2020), particularly for executive functions (Colcombe and Kramer, 2003; Angevaren et al., 2008; Voelcker-Rehage et al., 2011; Park and Bischof, 2013; Kaushal et al., 2018; Stojan and Voelcker-Rehage, 2019). These benefits have been attributed to numerous and overlapping neurobiological adaptations, including higher gray matter volume (Voelcker-Rehage and Niemann, 2013; Erickson et al., 2014) and preserved white matter structure (Tseng et al., 2013; Sexton et al., 2016; Kim et al., 2020), increased cerebral blood flow and vascularization (Sonntag et al., 2007; Tarumi and Zhang, 2018; Bliss et al., 2021), as well as improved connectivity between brain regions (Voss et al., 2013, 2015). Executive functions might particularly benefit from these structural and functional brain changes as they depend on a distributed neural network across different brain regions (Niendam et al., 2012; Diamond, 2013). Especially (pre)frontal areas, but also other brain regions in the parietal and temporal cortex, are associated with executive functions (Alvarez and Emory, 2006; Shokri-Kojori et al., 2012). Even though these brain areas are quite vulnerable to the effects of age, they are also sensitive to the beneficial effects of physical fitness/activity (Bherer et al., 2013; Gomez-Pinilla and Hillman, 2013; Voelcker-Rehage and Niemann, 2013). Thus, higher physical fitness/activity may facilitate the neural basis of executive functioning in particular. In addition, executive functions also seem to profit from higher cognitive processing speed. Cognitive processing speed is also largely associated with white matter structure (Kerchner et al., 2012; Kuznetsova et al., 2016). As such, well-preserved white matter integrity and myelination enable faster signal transmission, thus further strengthening the effective integration of executive functions. These described effects of physical activity/fitness on cognitive and brain function, however, seem to differ not only with respect to the cognitive dimension but also with respect to the physical dimension (Colcombe and Kramer, 2003; Voelcker-Rehage et al., 2011; Voelcker-Rehage and Niemann, 2013; Barha et al., 2017; Ludyga et al., 2020). As such, cardiovascular and motor coordinative fitness have been attributed to distinct neurobiological mechanisms that seem to promote specific cognitive functions (Black et al., 1990; Voelcker-Rehage and Niemann, 2013; Tarumi and Zhang, 2018; Walsh and Tschakovsky, 2018; Walsh et al., 2020). Therefore, associations between physical fitness and specific cognitive functions often vary across studies and yet have to be investigated more systematically.

Put together, the extant literature suggests that driving behavior depends on fluid cognitive functions and that cognitive demands increase when executing an additional task during driving. The same fluid cognitive functions that are required for driving might benefit from cardiovascular and/or motor coordinative fitness in older adults. Therefore, the association of physical fitness with fluid cognitive functions may establish a positive indirect relationship between fitness and driving performance, particularly in cognitively demanding conditions (e.g., during dual-tasking). Higher cardiovascular and motor coordinative fitness, thus, may indirectly facilitate driving performance through higher cognitive functioning. Direct effects of physical fitness on driving, in turn, seem less conceivable, as driving a car is a physically low-demanding, sedentary behavior (with or without an additional task). Therefore, while previous studies only have focused on direct relationships between the described variables, in the current study we focused specifically on determining the described indirect relationships.

In this study, we hence aimed to examine the additional benefits that higher cardiovascular and/or motor coordinative fitness potentially yield for car driving performance in cognitively demanding conditions by mediation through cognitive functions. To mimic the varying cognitive demands of everyday car driving, a realistic virtual driving scenario that included a battery of additional tasks was implemented (see "Driving Simulator Setup and Scenario" section). The rationale for using a driving simulator was to provide a safe virtual environment in which participants can engage in complex and potentially hazardous (dual-task) situations while driving (Bock et al., 2018). In addition, virtual environments can be fully controlled regarding the implementation of additional tasks as well as environmental conditions such as ambient light, traffic sounds, other traffic participants, or weather (Bock et al., 2019a). A driving simulator, thus, ensured the same conditions for all participants. The experimental outcome was evaluated by path analysis to determine the complex relationships between driving, fluid cognitive functions, and physical fitness (for further information see "Statistical Approach" section). The primary outcomes of interest in driving were: (1) variability in lateral car position (Latpos SD) as an indicator of *lane keeping*, and (2) mean velocity (Velocity M) as an indicator of *speed control*. Both parameters are common measures of driving performance and were found to be particularly sensitive to driving under dual-tasking conditions in previous studies (Papantoniou et al., 2017; Wechsler et al., 2018; Depestele et al., 2020; Stojan and Voelcker-Rehage, 2021). Four fluid cognitive functions (inhibition, shifting, updating, cognitive processing speed) were assessed and set separately as intermediate dependent variables in our path model (see "Statistical Approach" section and **Figure 1**). In addition, two indicators of physical fitness were entered as separate independent variables into the model, i.e., cardiovascular fitness (cardiorespiratory capacity *via* peak oxygen consumption) and motor coordinative fitness (composite score of static balance, psychomotor speed, bimanual dexterity). We assumed differential associations between various cognitive functions and driving performance, and differential relationships of cardiovascular and motor coordinative fitness with cognitive functions. According to our main research question, we hypothesized a positive indirect effect of both cardiovascular and motor coordinative fitness on driving performance *via* indirect pathways through fluid cognitive functions. Furthermore, we also expected distinct indirect effects of cardiovascular and motor coordinative fitness on driving performance based on their differential neurobiological mechanisms and relationships with cognitive functions. This is the first study to examine the indirect benefits of physical activity/fitness on dual-task driving in healthy older adults.

MATERIALS AND METHODS

Study Design and Participants

For the purpose of this study, data from two phases of a larger project (from here on referred to as project phase I and project phase II) were combined to ensure sufficient statistical power for the proposed model. Both data sets were collected as part of the DFG (German Research Foundation) Priority Program SPP 1772 "Multitasking". Some data from project phase I have been already published elsewhere (Wechsler et al., 2018; Bock et al., 2019b), and other data will be published later on. In total, data from 120 healthy older adults between 64 and 79 years of age (M = 69.56 ± 3.62 years, f = 53) were pooled (sample 1, n = 61, sample 2, n = 59). Demographic characteristics of the two samples are presented in **Table 1**, indicating that both samples were comparable regarding age, sex distribution, education, body mass index (BMI), and cognitive status. Study designs, recruitment strategies, inclusion/exclusion criteria, and applied tests were largely similar between project phases. Therefore, the two samples of project phase I and II should be considered cohorts of the same population. Community-dwelling, healthy older adults were recruited *via* public advertising, including radio reports, newspaper articles, flyers, and senior college talks. Participants were screened for eligibility during a structured phone interview lasting for 10–15 min. All inclusion criteria were self-reported and comprised the following conditions: Aged between 65 and 75 years [minor exceptions for spouses, n = 5: aged 64 (n = 1), 78 (n = 1), and 79 (n = 3)], BMI < 30, absence of physical (e.g., cardiovascular or orthopedic conditions), neurocognitive (e.g., dementia or traumatic brain injuries), or psychological (e.g., depression or anxiety disorders) medical conditions, regular driving activities during the last 6 months (at least one time per week), being able to walk for at least 30 min without any assistance. In the sample of project phase I, left- and right-handers were included (n = 5 left-handers), while in the sample of project phase II left-handers were excluded (exception for spouses, n = 3 left-handers). All participants self-reported normal or corrected to normal vision and hearing. After the eligibility check, further screening tests were applied including the Freiburg Visual Acuity Test v. 3.9.0 (cut-off: 20/60; Keeffe et al., 2002) and Mini-Mental-State-Examination (cut-off: 27/30; Creavin et al., 2016). No participant had to be excluded based on these tests. Furthermore, all participants had to obtain medical clearance and consent from their practitioner/cardiologist to participate in this study (exercise electrocardiography). All participants received monetary compensation (15*e* per testing day). The ethics committee of the German Sport University, Cologne, Germany approved project phase I (Nr.: 27/2015), and the ethics committee of the Chemnitz University of Technology, Germany approved project phase II (Nr.: V-280-17-CVR-Multitasking-29062018). Both project phases were conducted in accordance with the latest version of the Declaration of Helsinki (World Medical Association, 2013). All participants signed an informed consent statement before testing.

TABLE 1 | Participants' demographic information.

	project phase I, n = 61 M (SD) or n	project phase II, n = 59 M (SD) or n	t or x^2	p (uncor.)
Age (years)	69.93 (2.95)	69.17 (4.20)	1.15	0.253
Female/Male (n)	23/38	30/29	2.10	0.147
Education (years)	15.62 (3.21)	15.77 (2.57)	−0.27	0.780
Height (in m)	1.72 (0.09)	1.69 (0.08)	2.39	0.019
Weight (in kg)	74.76 (10.80)	70.92 (9.18)	2.10	0.038
BMI (kg/m^2)	25.08 (2.44)	24.91 (2.85)	0.36	0.719
MMSE (0–30)	29.15 (1.00)	29.21 (0.85)	−0.35	0.730

Note. Means (M) and standard deviations (SD in parentheses) are presented. BMI, body mass index; MMSE, mini-mental state examination; Uncorrected p-values are presented.

Measures

Driving Simulator Setup and Scenario

Driving behavior was assessed using commercially available driving simulator hardware and software (Carnetsoft® version 8.0, Groningen, The Netherlands). The driving simulator consisted of three 48″ monitors (laterally angled at 45°) on regular desks with a horizontal field of view of 195° (for a graphical illustration of the setup, see Wechsler et al., 2018). A VW golf seat, Logitech G27 steering wheel (Logitech International S.A., Lausanne Switzerland), and gas and brake pedals were located at positions similar to a real car, and a conventional numeric keypad was mounted on the right side near the steering wheel. Numbers from 1 to 6 were visible on the keypad (two rows with three numbers), other keys were covered with black tape. A head set was used for task presentation and characteristic driving sounds. The seat and gas and brake pedals were individually adjustable to fit every participant's comfortable driving position. Motion sickness was minimized by utilizing a research-grade simulator with wide-screen displays for smooth rendering of visual motion. The visual field around the displays was covered by black cloth to reduce perceptual conflicts between central and peripheral vision.

The driving scenario lasted about 25 min (25.7 km) and simulated a typical rural environment: a road that was slightly winding through a landscape consisting of grasslands, clouds, small trees, animal enclosures, hay rolls, construction sides, road signs, and gas stations. No intersections, traffic lights, cyclists, or pedestrians were included. Oncoming traffic comprised other cars and buses. Participants drove a VW Golf and followed a lead car. Another car followed at a reasonable distance behind the participant's car. The lead car was programmed to drive at 70 km/h and slowed down slightly when the distance with the driver exceeded 100 m. Participants were instructed to drive as they normally would, and to follow the lead car at a reasonable distance with a speed of 70 km/h unless other speed limits (i.e., 40 km/h during braking tasks) were specified. They were not allowed to pass the lead car, and they were told that no cars will pass them. Ten braking sections were included in the driving environment. When reaching one of those sections, the lead car briefly braked: it slowed down to 40 km/h for about 6 s and then sped up again to 70 km/h. Braking sections, however, were not further considered in the present study, and they did not overlap with the additional tasks outlined below. If the participants' car crashed (e.g., into the lead car or oncoming traffic, rarely a cow/tree), the front window shattered (including acoustic feedback) and the driver's car was relocated between the rear and lead car. Participants practiced driving for 3–4 min (driving only) in the same environment used for data acquisition. They also practiced the additional tasks for 3–4 min (tasks only) while their car drove in autopilot mode in the same environment. Participants did not practice dual-task driving. Instructions on driving and additional tasks were provided verbally. All participants followed instructions correctly during practice trials and during data acquisition, without asking for repetitions or for slower speech. From this, we concluded that their language comprehension and hearing was not overly degraded.

During driving, participants executed different additional tasks. These tasks were modeled after typical real-life activities often performed during driving. To increase realism and to mimic the varying demands of everyday car driving, we provided different stimulus modalities (visual input on the windshield = in-vehicle display, auditory input *via* headphones = passengers, radio, or GPS), cognitive-motor task loads (i.e., baseline driving = no task, typing = dashboard operations, reasoning = conversation with passengers), and response modalities (typing = visuomotor responses, reasoning = verbal responses; Bock et al., 2018, 2019a). The number of trials (total trials $N = 60$) was equally distributed across the different task types and presentation modalities in both project phases. Tasks were scheduled in a mixed order and at irregular distance intervals. The driving scenario and the order and type of additional tasks was identical for all participants within each project phase (same seed; Bock et al., 2019a). Participants were instructed not to prioritize the driving or the additional task, but to respond as fast and as accurately as possible to the additional task. The following tasks were utilized:

The *reasoning task* required participants to verbally state an argument for or against an issue of general interest (e.g., "state an argument against using electric cars", in German language). Requests were limited to 10 words per sentence (max. 80 characters, 54 pt. font size, max. two lines) and could not be simply answered with "yes" or "no". The visual presentation lasted 5 s, auditory presentation varied between 3 and 4 s. Participants were instructed to respond verbally while continuing to drive. Answers were assessed as valid/not valid and protocolled by the experimenter. The *typing task* required participants to enter a 3-digit number (e.g., "345") into the numeric keypad to the right of the steering wheel. Only numbers consisting of the digits 1–6 were presented, and only those digits were accessible on the keypad. The visual presentation lasted 5 s, auditory presentation lasted about 3 s. The numbers entered and reaction times for each number were recorded digitally by the software.

Only in project phase I an additional memorizing task was used that was presented similar to the two tasks described above. Participants had to memorize and compare gas station prices (visual) and traffic news (auditory), respectively. In project phase II the memorizing task was removed and replaced with trials of the reasoning and typing task to keep the total number of $N = 60$ trials the same. For the current analysis, we, therefore, used data only from the reasoning and the typing tasks excluding the memorizing task from all further analyses. Driving performance data, including lateral car position and velocity of the participants' car, were recorded at 10 Hz. Preprocessing is detailed below (see "Driving Behavior" section). Performance of the additional tasks (reasoning and typing) was not evaluated in this study as we were only interested in driving behavior.

Cognitive Functions

Fluid cognitive functions were assessed by computer-based tests adapted from literature, all of which were programmed in E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA, USA). Each test took about 10 min. Stimuli were presented on a 24″ monitor (1,920 × 1,080 screen resolution). All stimuli were black and presented on a white screen background. Standardized instructions were displayed first, followed by up to three practice runs. Response feedback was provided after practice trials, but not after registered trials. All tests comprised six blocks of stimuli that were separated by inter-block breaks of 5 s (20 s after block 3). The response-stimulus interval was 800–1,200 ms; if there was no response on the preceding trial, the response-stimulus interval started after 2,000 ms. Participants responded by pressing the "X" or "M" key on a German keyboard with their left and right index finger. They were instructed to respond as fast and as accurately as possible. The reaction time of correct responses (RT) and the percentage of correct responses across all presented stimuli (ACC) were analyzed.

A visuospatial *n-back test* (2-back) was used to measure *updating of working memory* ("updating"; Schmiedek et al., 2009). Each block comprised a total of 19 dots that were sequentially presented for 500 ms in one field of a black 4 × 4 grid. Participants were asked to press the "M" key if the current dot appeared at the identical position as the dot two trials before (target), and to press the "X" key if the dot appeared at a different position (non-target). The first two stimuli of each trial were discarded from the analysis.

The *Simon test* was administered to measure *inhibition* (Simon and Wolf, 1963; Simon and Rudell, 1967). Each block included a total of 32 trials of left- or rightward pointing arrows that were sequentially presented for 500 ms to the left or right of a centered fixation cross. For 50% of the trials, the direction and position of the arrow were congruent (e.g., rightward arrow on the right side); for the other 50% of trials, they were incongruent (e.g., rightward arrow on the left side). Participants were instructed to press the left key ("X") for leftward pointing arrows, and the right key ("M") for rightward pointing arrows.

A spatial *task switching test* was used to measure *shifting* (modified from Kray and Lindenberger, 2000). Each block included a total of 17 trials that were sequentially presented in the middle of the screen for 1,500 ms. Each stimulus was either a circle or a rectangle and was either small or big. Participants had to respond to either the size (A) or the form (B) of the stimuli in the order AA-BB-AA-BB-AA-BB-AA-BB-A. Participants had to

TABLE 2 | Overview of all tests and variables used for statistical analysis.

Variable	Test	Raw measures	Performance indicator
Cardiovascular Fitness (IV_{exo})	Spiroergometry	Oxygen uptake	VO_2 peak
Motor Fitness (IV_{exo})	Purdue Pegboard Test (1), One-Legged Stand Test with closed eyes (2), Feet Tapping Test (3)	Number of correct pegs within 30 s (1), Average standing duration (max. 20 s; 2), Number of correct crossings/taps within 20 s (3)	Composite score (mean of the *z*-standardized scores)
Updating (IV_{endo})	*n*-Back Test	RT, ACC	BIS
Cognitive Processing Speed (IV_{endo})	Simon Test	RT (only congruent)	RT
Inhibition (IV_{endo})	Simon Test	ΔRT, ΔACC	BIS
Switching (IV_{endo})	Task Switching Test	ΔRT, ΔACC	BIS
Speed Control (DV)	Virtual Driving Scenario	Car velocity	Mean velocity during additional task performance
Lane Keeping (DV)	Virtual Driving Scenario	Lateral car position on the lane	SD of the lateral position during additional task performance

Note. Summary of the variables used for path analysis (for further details please refer to section "Measures" and "Data Analysis"). ACC, accuracy (in %); ΔACC, |congruent − incongruent| (in ms); BIS, balance integration score (z-scaled); DV, dependent variable; endo, endogenous; exo, exogeneous; IV, independent variable; RT, reaction time (in ms); ΔRT, |congruent − incongruent| (in ms); SD, standard deviation; VO_2 peak, peak oxygen uptake (in l/min).

press the "X" key for small or circular stimuli, and the "M" key for big or rectangular stimuli. The first stimulus of each trial was not analyzed.

Cognitive processing speed was derived from the *congruent Simon test* condition. The congruent Simon test condition affords only simple reactions to the pointing direction (left/right) of arrows involving only little cognitive demand and therefore reflects simple cognitive processing speed.

Cardiovascular Fitness

Spiroergometry (ZAN600 CPET, nSpire Health, Oberthulba, Germany) on a stationary bicycle (Lode Corival cpet, Groningen, the Netherlands) was used to assess *cardiovascular fitness*. Participants were asked to avoid intake of caffeine and alcohol for 12 h and any vigorous physical activities for 24 h before testing. A ramp protocol was applied to test for submaximal exhaustion (Niemann et al., 2016; Hübner et al., 2019; Stute et al., 2020). Participants were instructed to maintain a cycling frequency between 60 and 80 revolutions per minute. In project phase I, participants started at 30 W initial load that increased progressively by 10 W (female) or 15 W (male) per minute. Participants of project phase II started at 10 W (female) or 20 W (male) initial load that increased progressively by 15 W (female) or 20 W (male) per min. Ramp protocols were preceded by a 3 min resting period and followed by a 5 min cool-down (1 min initial load, then no load). In total, protocols lasted about 15–20 min. Electrocardiography [ECG, recorded with a 10-lead ECG fully digital stress system; Kiss, GE Healthcare, Munich, Germany), breath-by-breath respiration (oxygen uptake (VO_2), carbon dioxide output (VCO_2)], heart rate, blood pressure (every 2 min), and wattage were continuously assessed. Further, the respiratory exchange ratio (VCO_2/VO_2) was simultaneously determined. A Borg's 'rate of perceived exertion' scale (6–20: "very easy" – "very difficult") was administered every 2 min to ask for perceived exertion during cycling. The protocol was stopped when participant's respiratory exchange ratio remained > 1.05 for at least 30 s or exceeded 1.10, upon volitional fatigue, or occurrence of risk factors (i.e., heart rate, HR > about 220-age, blood pressure >230/115 mmHg, dizziness, cardiac arrhythmia, or other abnormalities). The outcome measure was peak oxygen consumption (VO_2 peak), which has been proposed as a sufficient indicator of cardiovascular fitness (Rankovic et al., 2010).

Spiroergometry was supervised by an experienced sports scientist. In project phase I, the ramp protocol was preceded by an additional, less demanding, alternating 30 W/80 W protocol that was performed for approximately 10–15 min. Due to technical issues, five participants of project phase II were tested using a different spiroergometry device (Oxycon Pro, Erich Jaeger GmbH, Hoechberg, Germany); data, however, were comparable to the other participants following visual inspection and therefore were handled accordingly.

Motor Coordinative Fitness

Motor coordinative fitness was assessed with a battery of three standardized tests for different domains of motor coordinative fitness (Voelcker-Rehage et al., 2010). Before each test, participants were shortly familiarized with the procedure and were controlled for correct performance. Time was kept using a stopwatch. *The Purdue Pegboard Test* (Purdue Pegboard test, model 32020, Lafayette Instruments, Lafayette, IN, USA) was administered to measure *bimanual dexterity* (Tiffin and Asher, 1948; Tiffin et al., 1985). Participants were asked to plug as many metal pegs as possible into two parallel rows (maximum 25 holes) of the pegboard with both hands simultaneously, from top to bottom, and hole by hole. Three runs were performed, each timed at 30 s. The outcome measure was the number of holes with correctly placed pegs, averaged across the three runs. *The Feet Tapping Test* was used to measure *psychomotor speed* (Voelcker-Rehage and Wiertz, 2003; Voelcker-Rehage et al., 2010). Participants were seated on a stationary chair and instructed to tap with both feet simultaneously back and forth across a mid-sagittal line on the floor for a duration of 20 s. They were instructed to move both feet completely across the line, with both soles flat on the floor. The outcome measure was the number of correct crossings, as assessed with a hand clicker. The better of two runs was selected for analysis. The *One-Leg Standing Test* with eyes open and eyes closed was performed to assess *static balance* (Ekdahl et al., 1989). Participants looked straight ahead and stood on one leg, while slightly flexing the other leg, for a maximum of 20 s (self-initiated). Eight runs were performed, four runs with eyes open and then four runs with eyes closed (two runs each per leg). Time was stopped when participants put down their lifted foot, pressed together their legs, hopped, or opened their eyes during closed eyes balancing. Due to a very distinct ceiling effect for eyes open balancing, only eyes closed balancing was analyzed. The outcome measure was the standing duration, averaged across all four runs of eyes closed balancing (Michikawa et al., 2009).

Procedure

Before the first day of testing, all eligible participants received general information about the project, informed consent forms, and a questionnaire on demographics, handedness, driving, physical, and social activities, and health status. Testing was distributed across 4 days in project phase I and 2 days in project phase II where fewer tests were administered. Total testing time, including test instructions and small breaks, was 4 (project phase II) to 8 h (project phase I) per participant. For both project phases, the same measures of cardiovascular and motor coordinative fitness, fluid cognitive functions, and driving were used (for an overview cf. **Table 2**). The order of tests followed different pseudorandomized schedules, to take serial-order effects into account. Differences between measures were accounted for by standardizing test scores per project phase.

Data Analysis

Raw data were preprocessed with E-Prime 2.0 (cognitive functions) and R Studio v1.1.463 (R Core Team, 2020; cardiovascular and motor coordinative fitness, driving behavior) using the same routines for participants of both project phases.

Driving Behavior

Driving behavior under dual-task conditions was analyzed for time segments of 0–10 s after the onset of an additional task. Data from our previous studies suggested that the effects of additional tasks persist for about 10 s after task onset. In addition, this time range closely corresponded to the minimal inter-stimulus interval (M = 17.75, SD = 4.55) across all tasks in both project phases. Therefore, this also was the longest interval without any overlap between additional tasks. Outcome measures were the standard deviation of the mean lateral position of the participant's car on the lane (Latpos SD, in m) and the average velocity of the participant's car (Velocity M, in m/s). Both measures are commonly used in car driving research (Wechsler et al., 2018; Depestele et al., 2020; Stojan and Voelcker-Rehage, 2021). They were computed for all reasoning and typing trials. Outliers were excluded using the $\pm$3.29 SD criterion for each participant (Tabachnick and Fidell, 2007). Data were then averaged across all trials, including task types (reasoning, typing) and presentation modalities (visual, auditory). Missing data (Latpos SD: n = 3, Velocity M: n = 3) were imputed by regression imputation as part of the path analysis (see "Statistical Approach" section). As described above, the performance (RT, ACC) of the additional tasks while driving was not analyzed separately (for further information on the additional tasks see Wechsler et al., 2018; Stojan and Voelcker-Rehage, 2021).

Cognitive Functions

In the first step, RTs (ms) were removed if RT < 80 ms or RT >1,300 ms. Second, remaining RTs were outlier corrected using the $\pm$ 3.29 SD criterion for each participant. Updating performance was quantified as the mean RT and ACC across target and non-target trials. Inhibition performance was calculated from the RT difference between congruent and incongruent trials, and from the corresponding ACC difference. Shifting performance was computed as the difference value of switch trials (i.e., AB and BA) and repeat trials (i.e., AA and BB), again separately for RT and ACC. Finally, cognitive processing speed was determined as the mean RT of all congruent responses; ACC for cognitive processing speed was not considered, as it was close to 100% for congruent trials in all participants. For all cognitive tests, participants with ACC <55% were considered random performers, and their performance on that particular test was treated as missing data. Missing data (in total: updating: n = 14, inhibition: n = 1, shifting: n = 22, cognitive processing speed: n = 0) were imputed by regression imputation as part of the path analysis (see "Statistical Approach" section).

To account for a speed-accuracy tradeoff in updating, inhibition, and shifting tests, RT and ACC scores were converted into a standardized performance index, the balance integration score (BIS), using.

$$BIS = z(\mathrm{RT}) - z(\mathrm{ACC}) \quad (1)$$

BIS is considered to best account for the speed-accuracy trade-off compared to other approaches, as it puts equal weights on RT and ACC (Liesefeld and Janczyk, 2019). Finally, the inverse of BIS was calculated to facilitate interpretation, with higher scores indicating better performance.

Cardiovascular Fitness

VO_2 peak was determined by applying a moving average filter (lag 20, two-sided to avoid phase distortion) to the VO_2 continuous time series data in order to improve the subsequent peak detection by accounting for the typical breath by breath fluctuations. VO_2 peak was identified as the maximum value in the range of the highest complete performance level (wattage) achieved by the participant. The accuracy of the peak detection was visually inspected for every participant. In addition, we determined whether participants reached their submaximal performance level considering a VO_2 peak >1.5 l/min and a respiratory exchange ratio coefficient (>1.0) at their highest wattage level. If participants did not meet these criteria (e.g., due to lack of motivation), the VO_2 peak was specified as missing. Missing data (n = 23) were imputed by regression imputation as part of the path analysis (see "Statistical Approach" section).

Motor Coordinative Fitness

No outlier correction was applied to the performance scores described above. For each participant, an overall index of motor coordinative fitness was calculated as the mean of the z-standardized scores for psychomotor speed, static balance, and bimanual dexterity (Voelcker-Rehage et al., 2010; Niemann et al., 2016). Hence, all three measures were equally weighted. Missing data ($n = 3$) were imputed by regression imputation as part of the path analysis.

Statistical Approach

Path analysis was used to test the hypothesized linear relationships of our proposed model (**Figure 1**). Path analysis often is referred to as a special case of structural equation modeling (Jöreskog, 1970; Byrne, 2010; Tarka, 2018). It builds upon multiple regression and is applied to investigate complex relationships between dependent (endogenous variables) and independent variables (exogenous variables; Wright, 1934; Stage et al., 2004). As the main advantage of path analysis over basic multiple regression, it allows an estimation not only of direct effects between variables, but also an estimation of indirect effects mediated *via* one or multiple intermediate dependent variables.

Figure 1 illustrates our proposed model structure. Primary dependent variables were driving performance (Latpos SD and Velocity M). Intermediate dependent variables were cognitive functions (updating, inhibition, shifting, and cognitive processing speed). Independent variables were fitness domains (cardiovascular fitness and motor coordinative fitness). According to our hypothesized theoretical model, direct pathways were considered between driving performance and cognitive functions, as well as between cognitive functions and fitness domains. As described above, we hypothesized indirect but no direct pathways between fitness domains and driving performance. Direct and indirect pathways are displayed in **Figure 1**. Direct effects are depicted as solid lines. Indirect effects (labeled as 'IE') are depicted as solid lines passing the intermediate structure of cognitive functions as dotted lines.

The linear relationship between variables was tested simultaneously using path analysis with SPSS (version 26; IBM Corp., Armonk, NY, USA) AMOS 26.0 (Arbuckle, 2014). A missing value analysis was performed (Little's MCAR test; Little, 1988), indicating that data were missing completely at random ($\chi^2 = 73.33$, DF = 75, $p = 0.53$). Missing values (7.19% of all data) were handled through regression imputation (Acock, 2005; Madley-Dowd et al., 2019), by which missing data points are determined based on participants with similar values. Fit of the proposed model was assessed by comparative fit index (CFI), Tucker-Lewis Index (TLI), the standardized root mean square residual (SRMR), and root mean square error of approximation (RMSEA). Values exceeding 0.90 for the CFI and TLI, and values less than 0.09 and 0.08 for the SRMSR and RMSEA, respectively, are indicative of strong model fit (Marsh et al., 2004).

RESULTS

The proposed model (see **Figure 1**) gave a strong fit to our experimental data according to all criteria adopted, $\chi^2 = 11.30$, $df = 12$, $p = 0.418$; CFI = 0.98; TLI = 0.96; RMSEA = 0.015, 95% CI RMSEA = 0.000, 0.098; SRMR = 0.051. Standardized beta coefficients for the model pathways are presented in **Figure 1**.

Main effects—Cognition on Driving: Updating ($\beta = 0.19$, $p = 0.035$), but not Cognitive Processing Speed ($\beta = 0.11$, $p = 0.216$), Inhibition ($\beta = 0.07$, $p = 0.440$), and Shifting ($\beta = 0.11$, $p = 0.200$) predicted Latpos SD. Inhibition ($\beta = 0.23$, $p = 0.009$), but not Updating ($\beta = -0.04$, $p = 0.665$),

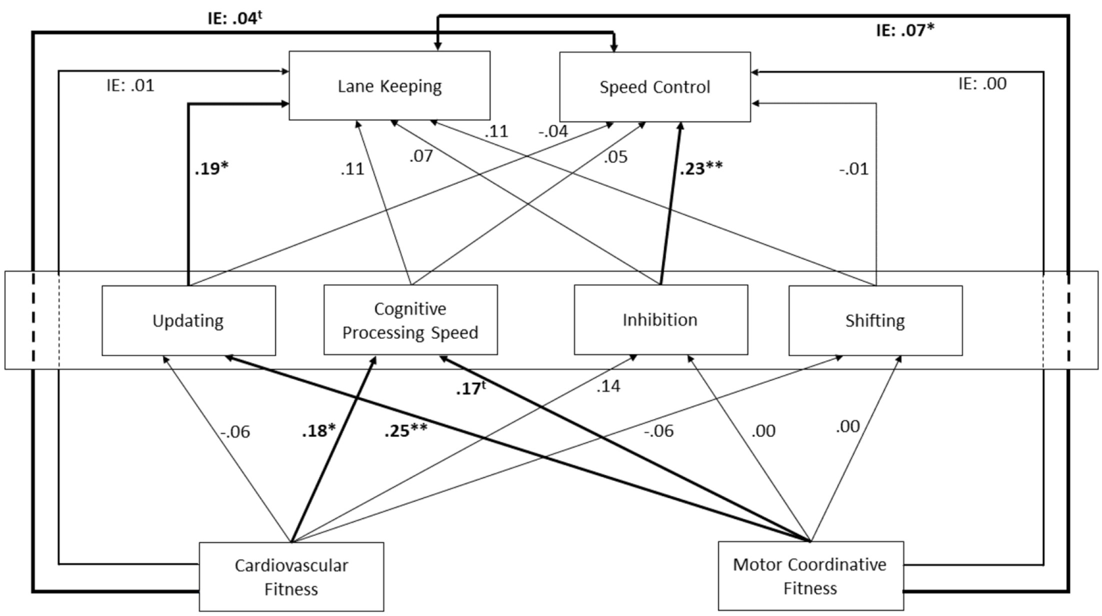

FIGURE 1 | Path diagram on the relationships between fitness domains (lower part), cognitive functions (intermediate part) and driving behavior (upper part). Bold arrows indicate significant ($p < 0.05$) or trend level effects ($p < 0.10$). Outer dotted lines indicate indirect effects (labeled 'IE') through cognitive functions. Note: *$p < 0.05$; **$p < 0.01$; $^t p < 0.10$.

Cognitive Processing Speed (β = 0.05, p = 0.599), or Shifting (β = −0.01, p = 0.882) predicted Velocity M.

Main effects—Physical Fitness on Cognition: Cardiovascular Fitness predicted Cognitive Processing Speed (β = 0.18, p = 0.039), but not Updating (β = −0.06, p = 0.499), Shifting (β = −0.06, p = 0.536), or Inhibition (β = 0.14, p = 0.123). Motor Coordinative Fitness predicted Updating (β = 0.25, p = 0.004) and Cognitive Processing Speed at trend level (β = 0.17, p = 0.053), but not Inhibition (β = 0.00, p = 0.962) and Shifting (β = 0.00, p = 0.982).

Indirect effects—Physical Fitness on Driving: Cardiovascular Fitness showed a trend-level indirect effect on Velocity M (β = 0.04, 95% CI 0.001, 0.097, p = 0.096), but no indirect effect on Latpos SD (β = 0.01, 95% CI −0.058, 0.079, p = 0.815). Motor Coordinative Fitness yielded a significant indirect effect on Latpos SD (β = 0.07, 95% CI 0.010, 0.133, p = 0.036), but no effect on Velocity M (β = 0.00, 95% CI −0.056, 0.050, p = 0.961).

DISCUSSION

In this study, we investigated whether physical fitness is positively associated with driving performance under dual-task conditions by mediation through cognitive functioning in healthy older adults. We hypothesized an indirect pathway by which two domains of physical fitness, i.e., cardiovascular and motor coordinative fitness, facilitate cognitive functioning (i.e., updating, shifting, inhibition, and cognitive processing speed) and thus driving (i.e., lane keeping, speed control) while performing cognitively demanding tasks. In accordance with extant literature, we observed that driving behavior and cardiovascular and motor coordinative fitness were directly related to specific, but different, fluid cognitive functions. As a result of these direct relationships and in accordance with our hypothesis, we found that motor coordinative fitness demonstrated a significant indirect effect on lane keeping, but not on speed control. Cardiovascular fitness, in contrast, showed a trend-level indirect effect on speed control, but not on lane keeping. Hence, being physically fit in older age seems to promote cognitive functions that are positively associated with driving and may therefore benefit car driving performance in older adults.

Direct Relationships Between Cognition and Driving Under Dual-Task Conditions

Cognitive functions were related to driving behavior in cognitively demanding conditions in the current study. Updating was associated with lane keeping, while inhibition was related to speed control. Speed control requires attentional and anticipatory control mechanisms to avoid collisions with a lead car, specifically when engaging in an additional, distracting task during driving. Attentional and anticipatory processes, in turn, are related to inhibition (Diamond, 2013; Elchlepp et al., 2016; Grandjean et al., 2019). Hence, impaired inhibition in older drivers might be associated with inferior attentional and anticipatory processes leading to poorer speed control (Anstey and Wood, 2011; Fofanova and Vollrath, 2011; Hahn et al., 2011; Karthaus and Falkenstein, 2016). This might become even more visible in a distracting or cognitively demanding driving condition. Lane keeping, in turn, requires sustained situational awareness and continuous monitoring and updating of visuospatial information of the environment (e.g., road winding; Papantoniou et al., 2017; Nilsson et al., 2020). Performing an additional task during driving typically increases cognitive load, thus limiting available cognitive resources. Additional tasks may cause interference effects on lane keeping due to limited updating capacity in older adults (i.e., capacity interference; Son et al., 2011; Pettigrew and Martin, 2016; Nilsson et al., 2020). Furthermore, when additional tasks require similar cognitive and perceptual resources, interference effects (i.e., structural interference) are typically more pronounced (Heuer, 1993; Liu and Ou, 2011; Stelzel and Schubert, 2011; Engstrom et al., 2017; Leone et al., 2017; Stelzel et al., 2017; Wechsler et al., 2018; Bohle et al., 2019; Perlman et al., 2019). Individuals with lower updating capacity hence show higher interference effects on lane keeping during driving when engaging in an additional task.

The observed relationships between cognitive functions and driving behavior, however, were quite specific and rather small. A recent systematic review also found that cognitive functions associated with driving behavior in younger and older adults were quite inconsistent across studies (Depestele et al., 2020). For older adults, some studies demonstrated such a relationship (Andrews and Westerman, 2012), while others did not (Park et al., 2011; Chen et al., 2013; Eudave et al., 2018). Varying relationships between cognitive functions and driving parameters might be attributed to different driving settings, task designs, and outcome measures (Park et al., 2011; Bunce et al., 2012; Eudave et al., 2018). In addition, driving experience may also influence cognitive demands during driving. Higher driving experience typically leads to generally less cognitive involvement during driving due to higher automatization (McKenna and Farrand, 1999; Harada et al., 2007; Charlton and Starkey, 2011). Assuming that our samples of older adults were quite experienced drivers (based on our inclusion criteria), cognitive demand during driving may have been reduced compared to more inexperienced drivers, such as younger or middle-aged adults or less experienced older drivers (Mourant and Rockwell, 1972; Lee, 2008; Emerson et al., 2012). Furthermore, experienced drivers may perform additional tasks more frequently while driving or use compensation strategies more efficiently, resulting in some degree of automation in these tasks as well, thus leading to less involvement of cognitive functions (Divekar et al., 2012; Klauer et al., 2014; Karthaus and Falkenstein, 2016; Pope et al., 2017). However, further research is needed to address additional factors influencing cognitive mechanisms associated with driving behavior, in particular for dual-task driving scenarios (Depestele et al., 2020).

Direct Relationships Between Fitness and Cognition

We observed direct relationships of cardiovascular and motor coordinative fitness with specific fluid cognitive functions. Cardiovascular fitness was related to cognitive processing speed only, whereas motor coordinative fitness was associated with cognitive processing speed and updating. This is at least partly in line with previous experimental findings and review studies. Results typically vary between studies, potentially as a result of, for example, different study designs, sample characteristics, or cognitive measures (Voelcker-Rehage et al., 2010; Hötting and Röder, 2013; Voelcker-Rehage and Niemann, 2013; Bherer, 2015; Dupuy et al., 2015; Kawagoe et al., 2017; Mekari et al., 2019). The effects of motor coordinative fitness on cognitive functions seem to be more pronounced than for cardiovascular fitness (Angevaren et al., 2008; Johann et al., 2016; Ludyga et al., 2020). This is in line with a current meta-analysis indicating higher benefits of exercise on cognitive functioning after motor coordinative exercise compared with other exercise types (Ludyga et al., 2020). Even though motor coordinative fitness has received far less scientific attention than cardiovascular fitness, the underlying mechanisms of cognitive benefits are discussed to be quite distinct (Cotman and Berchtold, 2007; Forte et al., 2013; Voelcker-Rehage and Niemann, 2013; Netz, 2019). Cardiovascular fitness is assumed to mainly induce changes in brain metabolism associated with improved cerebral blood flow and vascularization (Sonntag et al., 2007; Smith et al., 2010; Dupuy et al., 2015; Tarumi and Zhang, 2018; Kleinloog et al., 2019). Motor coordinative fitness, to the contrary, seems to induce fewer metabolic changes, but be related to functional changes such as higher synaptic density and network connectivity (Black et al., 1990; Lee et al., 2013; Cai et al., 2014; Demirakca et al., 2016). These brain physiological changes appear to be rather global than specific for both types of fitness, even though effects seem to be most pronounced in frontal areas (Voelcker-Rehage and Niemann, 2013; Reuter-Lorenz and Park, 2014; Bherer, 2015). As a result, the differential mechanisms of cardiovascular and motor coordinative fitness might favor effects on specific cognitive functions such as executive functions, which are associated with mutual but also unique neural correlates (Miyake and Friedman, 2012; Friedman and Miyake, 2017). Also, cognitive processing speed was positively associated with both cardiovascular and motor coordinative fitness. Cognitive processing speed reflects a rather global and relatively region-unspecific, lower-level cognitive function and has been suggested previously to benefit more from physical activity/fitness than other cognitive functions (Salthouse, 1996, 2009; Chang et al., 2010; Albinet et al., 2012; Quigley et al., 2020) as the effects of physical activity/fitness are assumed to be quite global as well (Dustman et al., 1984; Hillman et al., 2002; Angevaren et al., 2008). Among the included executive functions, only updating was related to higher (cardiovascular) fitness. Updating has been associated with frontoparietal brain regions specifically (Smith and Jonides, 1997; Wager and Smith, 2003). The neural overlap with exercise-induced changes hence might be higher for updating than for inhibition or shifting (Collette et al., 2005), even though those functions also have been related to frontal but also parietal brain areas (Bissonette et al., 2013; Zhang et al., 2017). In order to understand the relationship between certain cognitive functions and specific physical fitness parameters, systematic investigations are required that are beyond the scope of the current article.

Indirect Relationships Between Fitness and Driving Under Dual-Task Conditions

Most importantly, both cardiovascular and motor coordinative fitness were found to yield an indirect effect on driving behavior during additional task performance. Those indirect relationships were based on the described direct associations of cardiovascular and motor coordinative fitness with cognitive functions, and the direct associations of cognitive functions with driving behavior. Even though the magnitude of those direct effects differed largely, the sum of them led to the hypothesized indirect relationships. Interestingly, cardiovascular and motor coordinative fitness were positively related to distinct driving parameters. Motor coordinative fitness was associated with lane keeping, while cardiovascular fitness was associated with speed control. As discussed above, cardiovascular and motor coordinative fitness are thought to promote cognitive functioning *via* distinct neurobiological mechanisms, thus, eventually leading to differential effects on specific cognitive functions (Black et al., 1990; Sonntag et al., 2007; Lee et al., 2013; Cai et al., 2014). Those cognitive functions, again, are differentially associated with specific driving behavior parameters (Depestele et al., 2020). These distinct relationships could explain the observed differential associations between fitness domains and driving behavior parameters. However, it should be noted that, overall, the observed effects (direct and indirect) were rather small (indirect effects: $ß$ = 0.00–0.07). Nevertheless, even small effects might be of practical relevance and could be associated with a reduced risk for accidents during everyday car driving in older age. As mentioned above, the observed effects might be even more pronounced in inexperienced drivers as they rely more on cognitive control during driving and additional task performance, and thus may show greater benefits from higher physical fitness. In addition, our samples of older individuals were very fit, both physically and cognitively, thus limiting the available variance to explain the hypothesized indirect effects. We assume that the indirect effects of physical fitness on driving behavior would have been even more pronounced in a sample with a broader range of physical fitness levels as usually observed for the direct effects on cognitive functions (Voelcker-Rehage et al., 2010; Voelcker-Rehage and Niemann, 2013; Bamidis et al., 2015). Furthermore, considering that several cognitive functions relevant for driving (Karthaus and Falkenstein, 2016; Depestele et al., 2020) have not been assessed in this study (e.g., visuospatial skill or attention), the observed indirect effects might rather underestimate the real effects of fitness on driving behavior. In conclusion, our findings indicate that maintaining a high level of cardiovascular and/or motor coordinative fitness may facilitate real-car driving in older adults, thus promoting mobility and an independent lifestyle in higher ages.

STRENGTH AND LIMITATIONS

In this study, we used an ecologically valid, virtual driving scenario with realistic additional tasks that are frequently performed during everyday driving. We believe that such a task setting is favorable over less realistic settings (e.g., passively observing driving scenes or studies using abstract laboratory tasks) to infer potential effects on real-life behavior. The first limitation of our study, however, regards the above-mentioned lack of measures of additional cognitive functions associated with driving behavior. As a result, the observed indirect effects are likely to be underestimated and should be complemented by studies using additional measures for cognitive functions. Similarly, the second limitation of this study is that we did not address the association of other physical domains, such as physical strength, on cognitive functions and driving behavior. Similar to cardiovascular and motor coordinative fitness, physical strength seems to be associated with cognitive functioning in older adults (Chang et al., 2011; Ludyga et al., 2020). Therefore, physical strength may also yield indirect benefits for driving behavior *via* improved cognitive functioning. A third limitation concerns the analysis of fixed sections of driving performance after task presentation. The effects of additional tasks on driving behavior are likely to vary in their duration between different types of tasks, but also between participants. Thus, those effects might be analyzed in more detail using adapted time spans rather than a uniform time window of 10 s. For example, time windows might be defined for each task and presentation modality separately, depending on the persistence of their individual effects on driving behavior. However, based on previous findings the effects of additional tasks on driving seem to be most distinct within the first seconds after task onset (Strayer and Drew, 2004). Hence, we chose to analyze driving performance closely after task onset, and we utilized a uniform time window as we were not interested in the specific effects of different tasks or presentation modalities in the current study.

CONCLUSION

For the first time, we demonstrated that both cardiovascular and motor coordinative fitness are indirectly associated with driving in presence of additional cognitive demands in healthy older persons. Specifically, motor coordinative fitness was associated with cognitive functions that are involved during lane keeping, while cardiovascular fitness was associated with cognitive functions that are involved during speed control. By way of these associations, being physically active/fit may reduce the risk of accidents in cognitively challenging driving situations. At a more general level, our findings demonstrate that fitness may promote complex real-life behavior in older persons by supporting cognitive functioning. These findings are in accordance with the view that cognitive benefits associated with higher cardiovascular and motor coordinative fitness indeed facilitate complex cognitive-motor behaviors of everyday life. Future research should include additional fitness parameters (e.g., physical strength), cognitive measures (e.g., attention, visuospatial skills), driving parameters (e.g., number of crashes, braking performance), or may investigate other real-life behaviors (e.g., wayfinding, "walking while talking") in addition.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. Requests to access the datasets should be directed to CV-R (claudia.voelcker-rehage@uni-muenster.de).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the German Sport University, Cologne, Germany (Nr.: 27/2015) and the ethics committee of the Chemnitz University of Technology, Germany (Nr.: V-280-17-CVR-Multitasking-29062018). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RS, NK, OB, and CV-R were responsible for conceptualization and methodology of the research question and data analyses of the current manuscript. RS and NH were responsible for investigation. RS carried out software for data preprocessing, data curation and visualization. Formal analysis was performed by RS and NK. RS and NK wrote the original draft. NK, OB, and CV-R critically reviewed and edited the manuscript. Project administration (overall project) was carried out by OB and CV-R, project administration (research question reported here) was carried out by RS and NK. Funding acquisition, resources, and supervision were provided by OB and CV-R. All authors contributed to the article and approved the submitted version.

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Effects of Open Skill Visuomotor Choice Reaction Time Training on Unanticipated Jump-Landing Stability and Quality: A Randomized Controlled Trial

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Adapting movements rapidly to unanticipated external stimuli is paramount for athletic performance and to prevent injuries. We investigated the effects of a 4-week open-skill choice-reaction training intervention on unanticipated jump-landings. Physically active adults (n = 37; mean age 27, standard deviation 2.7 years, 16 females, 21 males) were randomly allocated to one of two interventions or a control group (CG). Participants in the two intervention groups performed a 4-week visuomotor open skill choice reaction training, one for the upper and one for the lower extremities. Before and after the intervention, two different types of countermovement jumps with landings in split stance position were performed. In the (1) pre-planned condition, we informed the participants regarding the landing position (left or right foot in front position) before the jump. In the (2) unanticipated condition, this information was displayed after take-off (350–600 ms reaction time before landing). Outcomes were landing stability [peak vertical ground reaction force (pGRF) and time to stabilization (TTS)], and landing-related decision-making quality (measured by the number of landing errors). To measure extremity-specific effects, we documented the number of correct hits during the trained drills. A two-factorial (four repeated measures: two conditions, two time factors; three groups) ANCOVA was carried out; conditions = unanticipated versus pre-planned condition, time factors = pre versus post measurement, grouping variable = intervention allocation, co-variates = jumping time and self-report arousal. The training improved performance over the intervention period (upper extremity group: mean of correct choice reaction hits during 5 s drill: +3.0 hits, 95% confidence interval: 2.2–3.9 hits; lower extremity group: +1.6 hits, 0.6–2.6 hits). For pGRF (F = 8.4, p < 0.001) and landing errors (F = 17.1, p < 0.001) repeated measures effect occurred. Significantly more landing errors occurred within the unanticipated condition for all groups and measurement days. The effect in pGRF is mostly impacted by between-condition differences in the CG. No between-group or interaction effect was seen for these outcomes: pGRF ($F = 0.4$, $p = 0.9$; $F = 2.3$, $p = 0.1$) landing errors ($F = 0.5$, $p = 0.6$; $F = 2.3$, $p = 0.1$). TTS displayed a repeated measures ($F = 4.9$, $p < 0.001$, worse values under the unanticipated condition, improvement over time) and an interaction effect ($F = 2.4$, $p = 0.03$). Healthy adults can improve their choice reaction task performance by training. As almost no transfer to unanticipated landing successfulness or movement quality occurred, the effect seems to be task-specific. Lower-extremity reactions to unanticipated stimuli may be improved by more specific training regimens.

Keywords: open skill exercise, reactive coordination, integrative neuromotor training, injury prevention, anticipation, non-contact injuries, agility

INTRODUCTION

Adjusting athletic movements (e.g., jump landings) quickly and precisely to unanticipated external visual stimuli is a key demand in interceptive sports (Mache et al., 2013; Almonroeder et al., 2015). Multiple visual stimuli of the environment like positions as well as movements of the opponents, teammates, and equipment must be perceived and processed to initiate a proper motor response (Besier et al., 2001).

Suboptimal decision making and errors in coordination may delay the execution of follow-up actions and can promote injuries (Swanik et al., 2007). Failed landings after a jumping action with a strong external focus, like performing a header in football, represent one of the most common mechanisms of non-contact injuries, like anterior cruciate ligament (ACL) ruptures (Cochrane et al., 2007; Sugimoto et al., 2015). Previous evidence shows that tasks in which an athlete receive a visual cue indicating the side of landing or the direction of a subsequent cutting movement upon landing only briefly before ground contact result in different knee biomechanics, when compared to tasks allowing for sufficient pre-planning. These motor changes during unanticipated landing have been suggested to predispose non-contact ACL injuries (Almonroeder et al., 2015; Hughes and Dai, 2021). For the successful and safe execution of unanticipated athletic movements neuromuscular factors, inhibitory control, and cognitive flexibility (Giesche et al., 2019) have been suggested critical contributors. More detailed, feed-forward and feed-back motor control (Koga et al., 2010; Aerts et al., 2013; DuPrey et al., 2016) as well as cognitive factors, such as processing- and reaction-speed (Herman and Barth, 2016), and visual-spatial memory (Monfort et al., 2019) are named. Improving these abilities may thus lead not only to a better performance but also to a decrease in the injury risk.

To operationalize these landing stability related abilities previous investigations used feed-forward [e.g., peak vertical ground reaction force (pGRF) (Giesche et al., 2019)], as well as feed-back dependent [e.g., time to stabilization (TTS) (DuPrey et al., 2016)] measures. Both TTS and pGRF appear to be directly related to the risk of lower limb injuries (Bakker et al., 2016; DuPrey et al., 2016). In previous trials, decision making performance during unanticipated tasks has been measured by error count (e.g., landing in the wrong position) (Mache et al., 2013; Giesche et al., 2019). First evidence suggests that the ability to successfully react and adapt athletic movements (e.g., landing) to a visual cue under high time constraints rely on cognitive functions, such as working memory and cognitive flexibility (Giesche et al., 2019). The number of decision errors may therefore represent an indirect measure of task-related cognitive function.

As humans act as a single system and not as a compilation of isolated abilities, a combination of motor and cognitive ability training may be the most promising approach to improve unanticipated reactions to external stimuli. As a possibility of such "two for the price of one"-trainings, computerized open skill training devices are often selected (Galpin et al., 2008; Paquette et al., 2017; Wilkerson et al., 2017, 2021; Engeroff et al., 2019, 2020). In contrast to closed skill approaches, which are based on pre-planned movements, athletes in open skill training exercises must adapt their movements to unpredictable external stimuli (Wang et al., 2013).

Device-based open skill training interventions mostly apply choice-reaction drills, executed with either the lower or upper extremities. Lower extremity drills require the athlete to respond to external stimuli while maintaining balance and controlling the body's center of gravity. This approach seems to result in improved neuromuscular abilities like balance, postural control, and performance in a repeated change of direction task (Galpin et al., 2008; Paquette et al., 2017; Engeroff et al., 2020). On the other hand, upper extremity drills commonly require less balance control as the participants are positioned in a stable bilateral stance in front of the device. This allows them to immediately react to the stimulus without controlling or adapting their posture. Therefore, reaction speed in upper extremity drills seems to rely more directly on the cognitive processing of the stimulus, when compared to the lower extremity drills. This is supported by previous studies indicating that upper extremity drills lead to improved cognitive and visuomotor choice-reaction time (Wilkerson et al., 2017, 2021; Engeroff et al., 2019). As a result of the upper extremity reaction training, Wilkerson et al. (2017) further observed a reduced overall injury incidence.

Although based on the same principles (motor responds to an external stimulus), lower and upper extremity drills may lead to different effects due to different primary demands (Engeroff et al., 2019). Beyond a general need of randomized controlled studies on the effects of such trainings on performance, a direct comparison of upper and lower extremity drills is needed.

Therefore, this investigation compared the effects of an upper and a lower extremity visuomotor open skill choice reaction training on decision-making and landing stability in pre-planned and unanticipated jump landings.

We hypothesized that (1) both trainings lead to improved task specific performance, and that (2) the cognition-dominant upper extremity reaction training is more likely to affect decision making, whereas the neuromotor-dominant lower extremity reaction training is superior in improving landing stability.

MATERIALS AND METHODS

Study Design and Ethical Aspects

This is one part of a three-armed randomized, single-blind controlled experimental design. Other results of this study are already published elsewhere (Engeroff et al., 2019, 2020).

The study was approved by the local ethics commission (reference number: 2016-47). The investigation was conducted in accordance with the Declaration of Helsinki (Version Fortaleza 2013). Before participating in the study, each volunteer signed a written informed consent form.

Participants

We recruited healthy and physically active (>1 h of exercise per week, assessed by self-report; IPAQ-Short form, Hagströmer et al., 2006) individuals, aged between 18 and 40. Recruiting was undertaken through bulletins, social media, and local sports clubs.

Exclusion criteria were acute or chronic physical or mental illness, as well as injuries and substances abuse. Furthermore, participants were excluded if they had suffered a lower limb injury in the previous 6 months or had undergone surgery in the previous 12 months. Participants were asked to abstain from alcohol and caffeine and to refrain from physical activity for 24 h prior to the pre- and post-examination appointments. Participants were also asked to maintain their regular physical activity habits and regular diet during the study-period.

Experimental Setup

Participants were randomly allocated to one of the two intervention groups or the control group (CG). The randomization sequence was generated using BiAS 10.0 (BiAS for Windows, Frankfurt), a balanced block-randomization (n = 14 per block) was undertaken. The allocation was not concealed.

The two training groups participated in a 4-week open skill visuomotor choice reaction training for the upper or lower extremities. The training sessions were performed in a laboratory of the Institute and were supervised by two sports scientists.

Before and after the 4-week intervention period, all outcomes were assessed. Assessors were blinded to the participants' group allocation.

Intervention

Training frequency was: three sessions per week (at least 24 h break between each session) for a total of 12 sessions. Session duration was 20 min. The CG received no intervention.

Before each training session, participants performed a 2-min warm-up, consisting of jumping jacks (= repetitive jumping from neutral stance to a position with legs spread and hands touching overhead).

The training reaction drills were performed on a board (100 × 76 cm) equipped with five sensor pads (top right and left, bottom right, and left, center) connected to a control box that provided a visual stimulus and feedback information via five lights corresponding to the sensor pads (The Quick Board, LCC, Memphis, TN, United States). Galpin et al. (2008) confirmed the reliability of the device (ICC = 0.89).

In one session, three different sets of choice-response tasks were performed, with four trials each. The trials of the first set had a duration of 30 s, those of the second set of 15 s, while the ones of the third set lasted 5 s. Between trials, participants rested in a seated position for 60 s.

For lower extremity training, participants started in an upright position standing on the board. The control box was placed at a distance of 1 m in front of the participants at head level. The feet were positioned to the left and right of the board's central sensor. No sensor was touched in the starting position. For upper extremity training, the board was placed vertically in front of the participants at head level. The control box was placed between the two upper sensors. After a 5-s countdown, one of the five LEDs representing the sensor areas was activated on the control box. Participants were instructed to tap the respective sensor on the panel with their right or left foot/hand as quickly as possible. The two sensors on the right side had to be touched with the right foot/hand, the sensors on the left side with the left foot/hand. The middle sensor could be touched with either the right or left foot/hand. After a correct contact (placing the correct foot/hand on the indicated sensor pad), the participants had to return to the starting position and another light randomly turned on. The order and selection of the stimulus during all trials was randomized automatically by the device based on a rectangular probability distribution.

The goal of each trials was to achieve as many correct contacts as possible. The number of correct contacts was automatically recorded by the device. The setup of the training intervention for the upper and lower extremities is shown in **Figure 1**.

Jump Landing Tasks

The participants performed countermovement jumps (CMJ, hands on hips) with pre-planned and unanticipated split-stance landings.

The required landing position (left or right footprint representing the front foot of the split stance) was illustrated on a presentation slide (Microsoft PowerPoint, 2010) displayed on a screen (inch: 17), which was positioned 2 m in front of the participants at chest-height.

In the pre-planned trials, the required landing position was displayed before take-off. For the unanticipated condition, the required landing position was displayed at take-off. For that purpose, a single button USB switch (KKmoon; South Africa) was placed under the jump platform and connected to the laptop. At take-off, the USB switch was activated, leading to a slide change that provided the required landing position (120 ms delay).

In both the pre-planned and unanticipated condition, the participants landed on a capacitive pressure platform. They

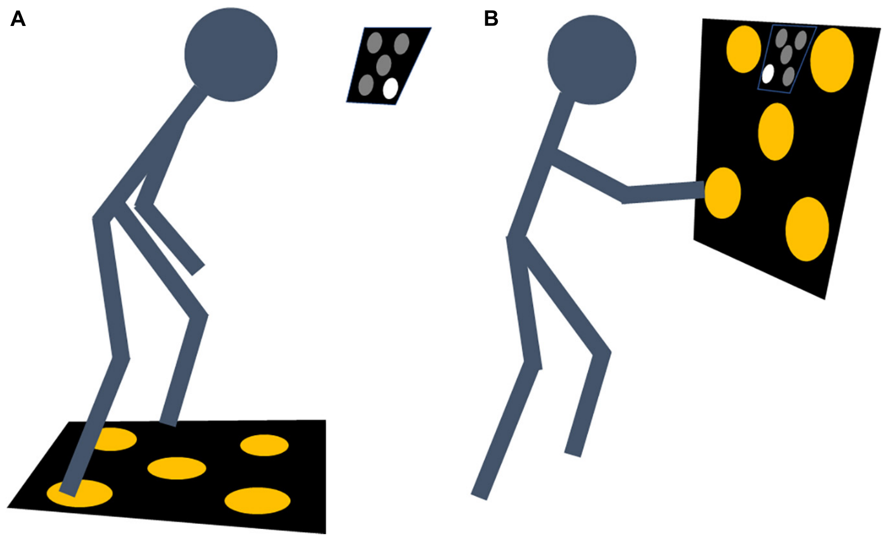

FIGURE 1 | Setup for the open skill visuomotor reaction drill of the lower **(A)** and upper **(B)** extremities.

landed in the required split stance position, aimed to regain a stable stance as quickly as possible, and maintaining this position (hands on hips and fixating a cross at eye-level) for the following 15 s.

To ensure that participants had sufficient time to make a choice-reaction decision (responding to the stimuli) during the jump, we instructed them to jump ∼25–30 cm high (approximately 400–500 ms). The corresponding available reaction time of ∼300–400 ms (flight time minus latency of the automatic stimulus presentation) was comparable to those of previous studies (Giesche et al., 2019). The participants practiced this target jumping height during a familiarization session (pre-planned: $n = 2$, unanticipated $n = 2$) right before the actual measurement. After each jump, we immediately provided them with feedback regarding their achieved flight times to adjust the jumping height, if indicated.

Within the subsequent jumps included in the evaluation, participants performed as many trials as they needed to achieve five successful landings within the pre-planned and unanticipated condition (max. 15 trials for each condition, inter-trial break: was 1 min).

Since wearing shoes, compared to barefoot, can have an impact on postural stability after jump landings, all participants were asked to wear solid sport shoes (Zech et al., 2015).

Outcomes

During the baseline examination, personal, and anthropometric data as well as the amount of habitual physical activity (IPAQ-Short form; Hagströmer et al., 2006) were assessed. The day of the week and the daytime of pre- and post-measurements were standardized for each participant. Nevertheless, we controlled the participants' self-reported arousal as a potential confounder. Self-reported arousal was assessed with a visual analog scale from 1 to 10 (Rodenbeck et al., 2001).

Training effects within the open skill visuomotor choice reaction task were operationalized using the mean of the absolute number of correct hits of three 5-, 15-, and 30-s trials.

The landing biomechanics were assessed by a 158 × 60.5 cm capacitive pressure platform (50 Hz, Zebris FDM, Zebris Medical GmbH, Isny, Germany). Gregory and Robertson (2017) reported the Zebris FDM pressure platform to be a valid instrument to assess balance in clinical and research setting ($r = 0.42–0.66$).

Landing stability was operationalized by the peak vertical ground reaction forces [pGRF; (N)] and TTS (sec; Wikstrom et al., 2005). The pGRF represents the maximum value of the recorded vertical ground reaction forces in the z-axis. The TTS describes the time required to regain a stable stance after the landings. According to Wikstrom et al. (2005) the stance is defined as stable as soon as the sequential average no longer exceeds the threshold of 0.25 SD of the overall mean ground vertical force. Kaliyamoorthy and Jensen (2009) reported a moderate to high reliability of the TTS. Data on pGRF and TTS were only analyzed for successful trials of the pre-planned and unanticipated landings.

To operationalize the decision-making quality within the unanticipated condition, an investigator documented the number of landing-decision errors (landing on the wrong leg) on an examination form. The jumping height of each trial was calculated via the flight time (assessed by the platform).

Statistical Analysis

Required participant sample size was estimated using G*Power (Version 3.1.9.2; Germany). Based on the effect size for visuomotor choice reaction training reported in Galpin et al. (2008; Cohen's d: 1.12), an alpha error probability of 0.05 and power of 0.8, we determined a required sample size of 11 participants for each of our three groups. Assuming a dropout rate of 10%, we aimed for a total sample size of 36 participants to be recruited.

All statistical analyses were performed per protocol using SPSS 23 (SPSS Inc., Chicago, IL, United States). Figures and tables were created using Excel 2010 (MS Office, Microsoft Corporation, United States). Results with an alpha-error probability below 5% were considered as statistically significant.

After the range data plausibility check the descriptive analysis was carried out. Mean values as well as standard deviation were calculated. Groups were compared using analysis of variance (ANOVA).

To analyze potential training induced differences between pre- and post-intervention performance between groups within the jump-landing task, a two-factorial (four repeated measures, three groups) ANCOVA was performed for each outcome. The three groups compared included the CG, the lower extremity intervention group as well as the upper extremity intervention group. As repeated measures the two conditions of the jump-landing task (anticipated, unanticipated) as well as the two measurement times (pre and post measurements) were selected. Flight time (difference between pre-planned and unanticipated jumps) and self-reported arousal were set as covariates. Ninety-five percentage confidence intervals of the covariate adjusted means of pre- and post-testing values were used to identify between-condition, time, group, and interaction effects. Confidence intervals not overlapping the mean of the respective comparator are considered significant.

All statistical analysis were conducted after corresponding assumption checks (Shapiro–Wilk test for normality, Levene test for variance homogeneity, linearity, and equal slopes).

RESULTS

Descriptive Data

Thirty-seven participants were included into the study. Study and participants flow is displayed in **Figure 2**. The collective and group-separated participant characteristics are shown in **Table 1**. Upper extremity intervention group and CG significantly differ in age ($t = 3.4$; $p = 0.003$). No further differences were found between the groups within the anthropometric and health-related data.

During the intervention, both training groups improved their performance in the 5-s (Upper extremity intervention group: +3.0 ± 1.8 hits; lower extremity intervention group: +1.6 ± 0.843 hits), 15-s (Upper extremity intervention group: +7.0 ± 2.8 hits; lower extremity intervention group: +4.0 ± 2.8 hits), and 30-s (Upper extremity intervention group: +16.3 ± 3.6 hits; lower extremity intervention group: +11.0 ± 5.3 hits) open skill visuomotor choice reaction drill. The weekly progress is displayed in **Figure 3**.

Jump Landing Outcomes

Peak ground reaction force showed significant repeated measures ($F = 6.5$; $p = 0.001$) but no group ($F = 0.4$, $p = 0.9$) or interaction ($F = 2.3$, $p = 0.1$) effects.

Post hoc, all groups tended to produce higher values under the unanticipated condition with a significantly difference for the CG in the pre-test measurement when compared to the pre-planned condition (CG: +17.4 ± 16.7%; Upper extremity intervention group: +20.4 ± 17.3%; Lower extremity intervention group: +14.8 ± 16.9%) (**Figure 4A**). Within the post-test measurements, no significant differences between the pre-planned and unanticipated condition appeared (CG: +12.8 ± 21.1%; Upper extremity intervention group: +13.1 ± 18.8%; Lower extremity intervention group: +8.6 ± 13.6%).

Time to stabilization displayed a repeated measures effect ($F = 4.9$, $p < 0.001$).

The lower extremity group showed an improvement over time in the pre-planned condition (CG: +0.6 ± 10.3%; Upper extremity intervention group: −5.2 ± 48.9%; Lower extremity intervention group: −4.7 ± 11.2%), leading to an interaction effect ($F = 2.4$, $p = 0.03$) (**Figure 4B**).

Between condition differences (unanticipated versus pre-planned landings) in TTS do not appear to be significant in pre- (CG: +1.1 ± 6.0%; Upper extremity intervention group: +4.4 ± 5.9%; Lower extremity intervention group: +1.9 ± 9.4%) and post-test measurements (CG: +4.9 ± 7.8%; Upper extremity intervention group: +1.4 ± 5.2%; Lower extremity intervention group: +4.6 ± 7.7%) (**Figure 4B**).

Decision making showed a significant repeated measures effect ($F = 21.8$; $p < 0.001$) but no significant between group or interaction effects ($F = 0.5$, $p = 0.6$; $F = 2.3$, $p = 0.1$).

Post hoc, all groups displayed a higher absolute number of landing errors in the unanticipated than in the pre-planned condition on pre and post testing day (**Figure 4C**). Finally, a time × covariate interaction was found for flight time and TTS ($F = 3.5$; $p = 0.031$). In addition, **Figure 4** shows a significant decline in the between condition differences (anticipated versus unanticipated) of the flight time following the lower extremity intervention. Absolute values of flight time (pre-planned; unanticipated) were: CG: Pre: 412 ± 60.6 ms; 447 ± 63.4 ms, Post: 414 ± 76.6 ms; 444 ± 64.0 ms; Upper extremity intervention group: Pre: 375 ± 63.3 ms; 418 ± 43.0 ms, Post: 395 ± 52.2 ms; 415 ± 38.0 ms; Lower extremity intervention group: Pre: 382 ± 58.1 ms; 433 ± 67.9 ms, Post: 398 ± 54.9 ms; 418 ± 53.6 ms. Self-reported arousal did not appear to systematically affect any outcome ($p > 0.05$). Values of the self-reported arousal on pre-test measurements were 6.9 ± 1.6 for the CG, 6.5 ± 1.6 for the upper extremity intervention group, and 6.3 ± 1.8 for the lower extremity intervention group. Within in the post testing day participants reported arousal values of 6.4 ± 1.7 in the CG, 7.4 ± 1.1 in the upper extremity intervention group, and 6.4 ± 1.4 in the lower extremity intervention group.

DISCUSSION

Both intervention groups improved performance within the specific lower or upper extremity open skill visuomotor reaction drill over the 4-week training period. These finding confirm our hypothesis 1.

We found no effect of the lower extremity intervention on the magnitude of the pGRF. However, a shorter TTS under the pre-planned condition after the 4-week lower extremity choice reaction training occurred, which is in line with hypothesis 2. Lacking effects of the upper extremity intervention on

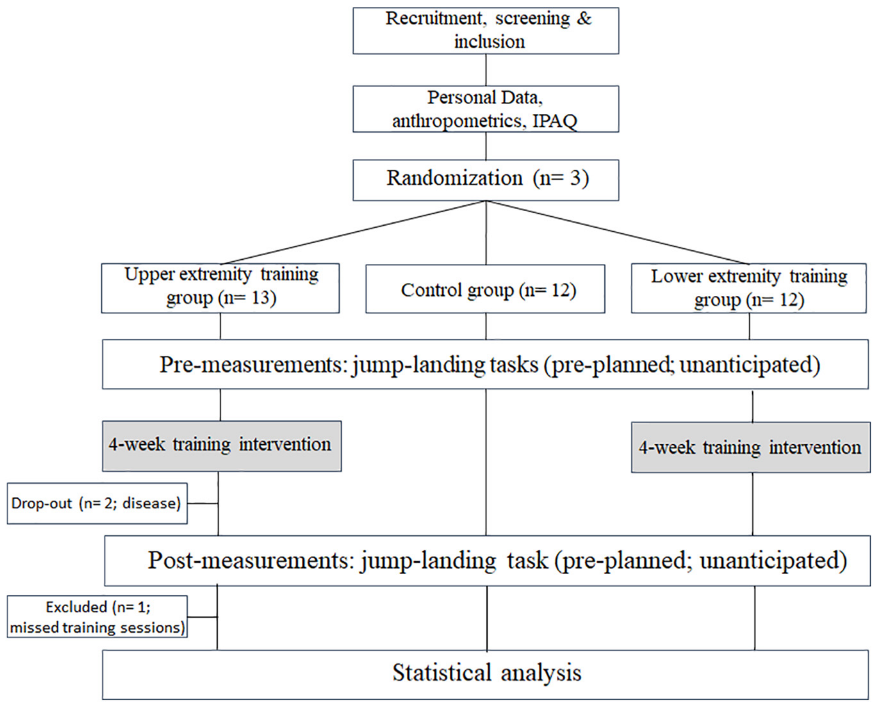

FIGURE 2 | Study and participants flow.

TABLE 1 | Anthropometrics and health related data of the study collective (separated by groups and total sample).

Outcome (mean, SD)	Total sample	Control group	Intervention group upper extremity	Intervention group lower extremity	Between group comparison (*F*-, *p*-value)
Age (years)	27.5, 2.7	29.1, 1.9#	26.3, 2.1#	27.2, 3.3	5.74, 0.01*
Body height (cm)	173, 10	174, 9.1	172, 12.4	172, 9.1	0.11, 0.89
Body weight (kg)	69.4, 12.1	72.9, 12.0	67.7, 13.7	67.7, 10.6	0.75, 0.48
BMI (kg/m^2)	23.2, 2.7	24.1, 2.9	22.8, 2.7	22.8, 2.4	0.93, 0.41
Physical activity (MET-hours/week)	46.8, 34.4	57.8, 45.9	45.7, 30.2	35.8, 18.7	1.28, 0.30

Means and standard deviation of the BMI, body-mass-index; cm, centimeter; kg, kilogram; m^2, square meters; MET, metabolic equivalent of task.
Significant between-group-differences ($p \leq 0.05$) are marked with an asterisk.
#Marks the groups which differ in age.

decision-making is in contrast to our assumption (hypothesis 2). Nevertheless, a significant reduction in the differences of flight time between the anticipated and unanticipated jump condition occurred after lower extremity training. Since this reduction of flight time did not lead to an increase in landing errors, this might indicate that subjects are able to react faster to a visual stimulus.

The finding of task-specific improvements after visuomotor reaction interventions is consistent with previous studies using the same device or similar devices. After 4-week choice reaction training with upper or lower extremities using the QuickBoard (The Quick Board, LCC, Memphis, TN, United States) Engeroff et al. (2019) found an increased performance within both intervention groups. Furthermore, the lower extremity intervention group improved in the upper extremity drill, but not vice versa. Galpin et al. (2008) and Paquette et al. (2017) confirmed this result regarding the training for lower extremities. Similarly, a visuomotor reaction training with the upper extremities on the Dynavision D2™ System, also led to significant improvements in task-specific performance.

With regard to landing-related outcomes of the present study, conflicting results appear. While the pGRF does not seem to be affected by both interventions, we found a decreased TTS in the pre-planned condition after the lower extremity training. The beneficial adaptation of the postural function is consistent with the results of previous studies. Galpin et al. (2008) found an improvement in pre-planned change of direction speed following 4 weeks of training. In addition, Paquette et al. (2017) found an improved balance and postural control within the star excursion test as well as during a single leg stance after a 6-week lower extremity choice reaction training. Again, the participants showed an enhanced repeated change of direction speed. These findings were confirmed by Engeroff et al. (2020), who found

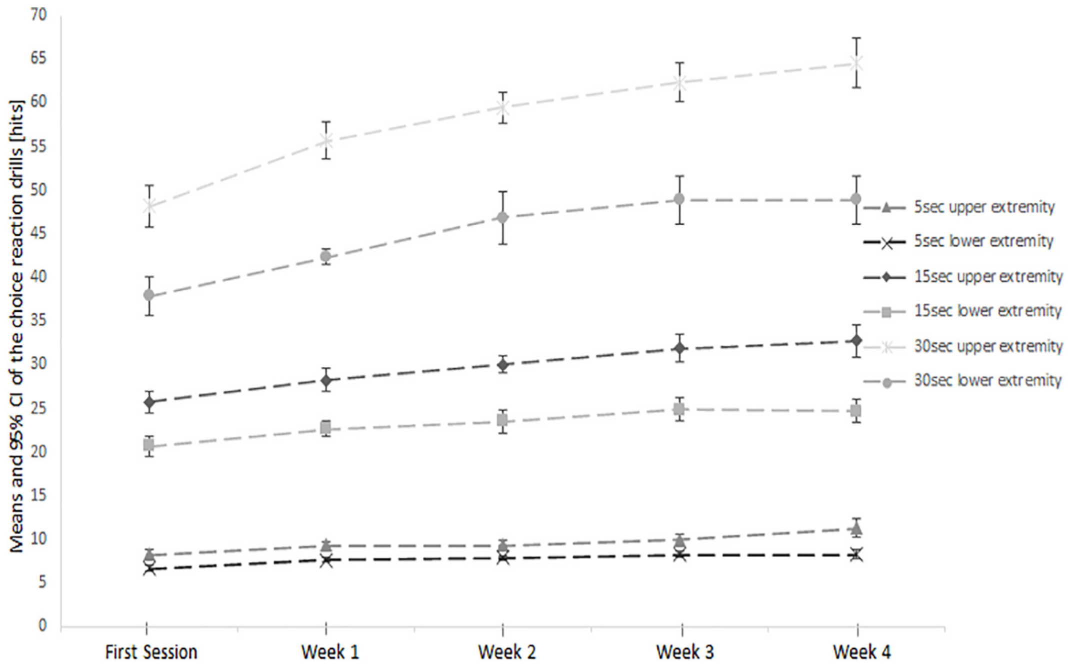

FIGURE 3 | Means and 95% confidence intervals of the absolute number of correct hits in the 15 s open skill visuomotor choice reaction drill during the 4-week training period.

an improvement within the hexagon change of direction test after a 4-week lower extremity choice reaction training. These results indicate that the decrease in the TTS might result from improved feedback and feedforward activation following the lower extremity training. The dynamic neuromuscular demands of the intervention may have led to improved postural control and faster recovery of the body's center of gravity after athletic movements. In contrast, with our collective and the methodology used, the pGRF does not appear to be sensitive enough to indicate potential effects of the intervention on landing stability regardless condition. Since pGRF is reached within the first 100 ms after ground contact, the improvements in feedback activation and postural control might not be manifested in this outcome (Koga et al., 2010). This result seems to be consistent with the meta-analysis of Lopes et al. (2018). In the context of neuromuscular injury prevention training, they found improvements in landing stability which, however, could not be represented in a reduction of pGRF.

The failed transfer into the unanticipated condition could be due to the high demands on neuromuscular performance and postural control in the lower extremity training intervention. In this training exercise, participants had to return to the starting position after each correct hit before responding to the next stimulus. Therefore, required time for processing and reacting to each stimulus is significantly longer then for the upper extremity drills. The resulting stimuli frequency in such training drills do not appear to reach the critical threshold level for potential neuronal adaptations (Engeroff et al., 2020). Non-specific motor-cognitive drills with complex motor demands and long response times might therefore not be the right choice to address reaction time performance. In contrast, upper extremity training could reach this threshold level but still has no effect on landing stability and landing errors due to missing neuromuscular components in the drills.

The lack of effects of the upper extremity training on the number of landing errors in the unanticipated condition may be due to the complex cognitive and neuromotor demands of the jump-landing task. Here, the participant must perceive an external stimulus, process it, and perform an appropriate lower extremity motor execution. This hypothesis is partly in line with the results of Engeroff et al. (2019), who found improved cognitive reaction time as a result of the same upper extremity reaction training approach, but no carryover to a lower extremity visuomotor reaction drill. The investigations of Wilkerson et al. (2017, 2021) and Williams et al. (2017) confirm the potential for improvements in visuomotor reaction performance following upper extremity choice-reaction training interventions. Williams et al. (2017) also found a significant reduction in core/lower extremity injuries in the following season.

In summary, on the one hand, the lower extremity training appears to increase neuromuscular performance but have only secondary cognitive effects. On the other hand, upper extremity training has a very small motor component but may induce cognitive adaptations. These could possibly not be represented in the number of errors due to lack of adaptations in the speed and quality of motor execution.

The finding of a reduced between condition differences (unanticipated minus pre-planned) in flight time without an increase in landing errors may indicate a transfer effect following the lower extremity training intervention. A reduction of the

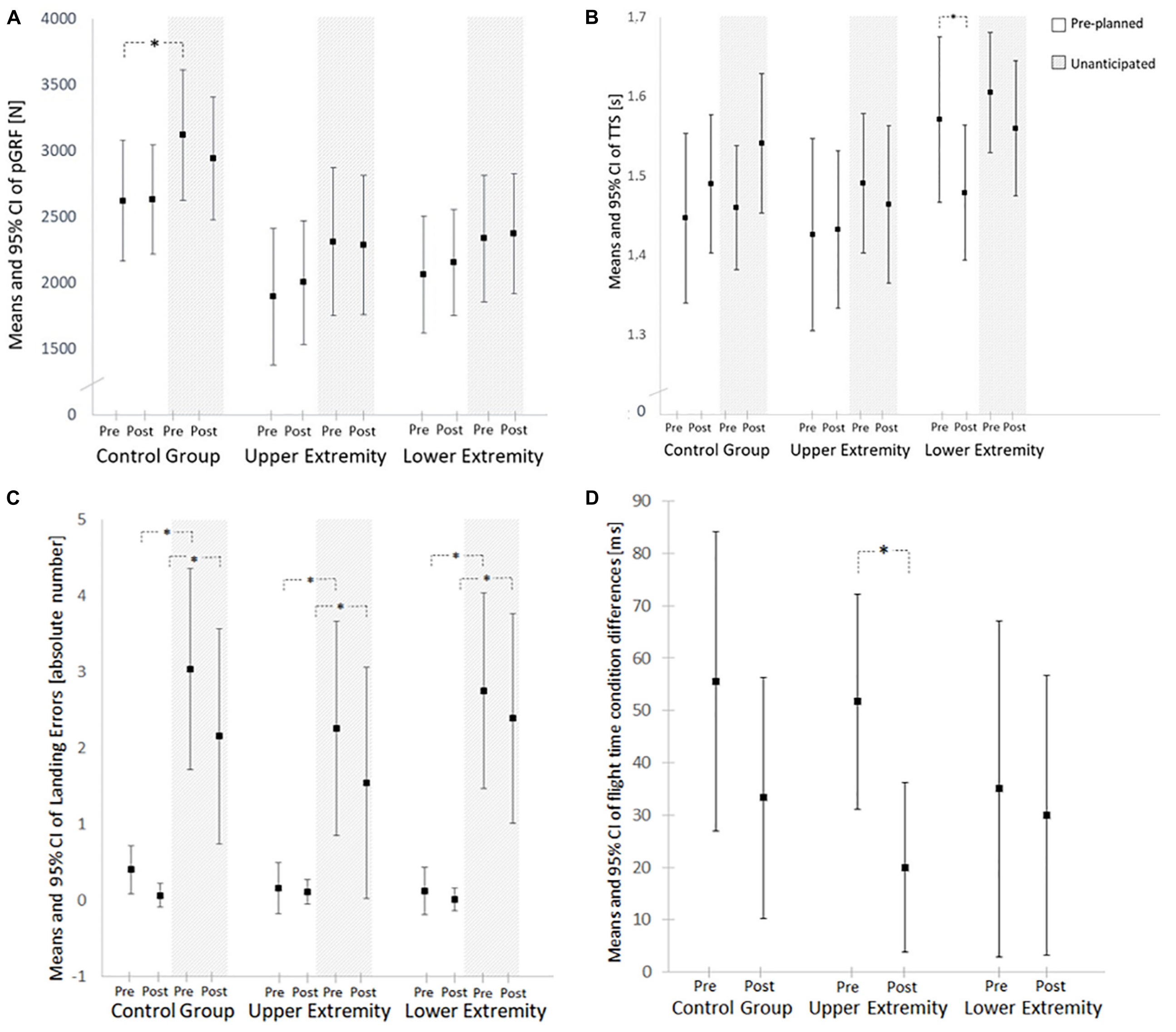

FIGURE 4 | Covariate adjusted means and 95% confidence intervals of the assessed parameters of pre-planned and unanticipated landings. **(A)** Peak ground reaction force (pGRF). **(B)** Time to stabilization (TTS). **(C)** Landing errors. **(D)** Flight time. N, newton; s, seconds; ms, milliseconds. Asterisk marks significant differences ($p \leq 0.05$).

flight time mean values within the unanticipated condition could be due to the participants feeling more confident in their decision making and/or motor execution, and therefore required a lower jump height (and therefore flight time). In terms of pre-planned jump landings, lower extremity training resulted in participants to choose the solution of a higher jumping height, confident in their improved landing stability.

Beside the treatment effects, we found a distinction in landing stability and decision making between the pre-planned and unanticipated conditions. All groups showed significantly more landing errors within the unanticipated landings in pre- and post-testing measurements. This finding confirms the existing evidence (Giesche et al., 2019). In addition, both outcomes for landing quality showed a trend for worse values in the unanticipated condition with significant differences in pGRF for the CG in the entrance examination. This is consistent with previous studies showing increased pGRF (Meinerz et al., 2015; Yom et al., 2019) during unanticipated athletic movements like jump landings or cutting maneuvers. Insufficient decision-making during athletic movement (Boden et al., 2009), as well as high pGRF (Hewett et al., 2005; Yu et al., 2006; Bakker et al., 2016) and lower postural stabilities (DuPrey et al., 2016; Giesche et al., 2019) upon landing or cutting in unanticipated tasks have been suggested to elevate the risk for non-contact lower limb injuries. This underlines the crucial role of both cognitive and neuromuscular performance for injury prevention open-skilled sports (Koga et al., 2010; Aerts et al., 2013; Herman and Barth, 2016; Giesche et al., 2019; Monfort et al., 2019).

Further studies need to investigate the effect of more sport-specific training paradigms that include more cognitive demanding neuromotor challenging exercises on task performance and injury prevention. Since neither of the two choice-reaction interventions led to improvements in movement quality and decision making within the unanticipated landings on its own, the effect of a combined intervention of motor-cognitive drills with different primary demands (e.g., combination of lower and upper extremity drills) could be examined.

Limitations

In this study, kinetic data were recorded. These can provide initial insights into the landing biomechanics. However, without kinematic analyses the results cannot be interpreted without doubt regarding the actual loading of the musculoskeletal system. For this purpose, e.g., 3D video recordings or motion capture could be added in future studies to capture joint angles and force moments. A considerable wide range in the flight times occurred (350–600 ms). This may have had an influence on the decision-making capability of each individual. Some participants used a bigger jump height (and therefore a longer flight time) as solution for solving the unanticipated jump-landing task. Because the available response time may affect the cognitive processing demands during the jump, it is difficult attribute potential cognitive improvements to the training intervention. The wide range of the 95% CI of the between-condition differences also demonstrate the heterogeneity of the study population (**Figure 4C**). Some subjects seem to prefer higher jump heights in the unanticipated condition, while others show similar flight times as in the anticipated condition. The wide range of the 95% CI of the landing errors also confirms the heterogeneity. While some subjects made only a few errors in the unanticipated condition, others seem to have had major problems with the cognitive-motor requirements.

The anticipated and unanticipated jumps are likely to reflect a repeated measure than a second within-subject design. Nevertheless, one may argue that performing a 2 × 2 × 3 ANOVA (instead of our 4 × 3 design) might be appropriate, likewise. This might led to slightly different results in the omnibus tests.

In terms of generalizability, our results give first indications of a transfer of lower extremity training to a sport-related jump-landing task. Nevertheless, this laboratory setting can only reflect the motor-cognitive demands of real game situations to a limited extent. Therefore, future studies should investigate the effect of such open skill reaction training on sport-specific movement patterns and injury risk indicators.

CONCLUSION

Our study showed that healthy adults can improve their upper and lower extremity choice-reaction performance by training. Nevertheless, the effect seems to be task specific. While the neuromuscular demanding lower extremity training improves postural stability after pre-planned landings, almost no transfer to decision making and movement quality within the unanticipated condition occurred.

Future studies need to clarify whether and in what context (e.g., rehabilitation, prevention, cognitive/neuromuscular diseases, athletic performance) such exercise paradigms are useful. Furthermore, it should be examined whether visuomotor interventions with more sport-specific stimuli and movements are superior to non-specific choice reaction trainings in terms of improving performance in unanticipated athletic movements.

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 Lokale Ethikkommission des FB05, Goethe-Universität Frankfurt am Main. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FG, TE, and DN developed the theory. TE and DF performed the computations. DN and DF performed the statistics and analyses, verified the analytical methods, provided a first manuscript draft, and took the lead in supervising the writing of the manuscript. DF and TE performed the measurements and outcome assessments. TE and DN supervised the findings of this work. All authors conceived of the presented idea, discussed the results, and contributed to the final manuscript.

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BRIEF RESEARCH REPORT
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Dynamic Functional Connectivity Signifies the Joint Impact of Dance Intervention and Cognitive Reserve

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Research on dance interventions (DIs) in the elderly has shown promising benefits to physical and cognitive outcomes. The effect of DIs on resting-state functional connectivity (rs-FC) varies, which is possibly due to individual variability. In this study, we assessed the moderation effects of residual cognitive reserve (CR) on DI-induced changes in dynamic rs-FC and their association on cognitive outcomes. Dynamic rs-FC (rs-dFC) and cognitive functions were evaluated in non-demented elderly subjects before and after a 6-month DI (n = 36) and a control group, referred to as the life-as-usual (LAU) group (n = 32). Using linear mixed models and moderation, we examined the interaction effect of DIs and CR on changes in the dwell time and coverage of rs-dFC. Cognitive reserve was calculated as the residual difference between the observed memory performance and the performance predicted by brain state. Partial correlations accounting for CR evaluated the unique association between changes in rs-dFC and cognition in the DI group. In subjects with lower residual CR, we observed DI-induced increases in dwell time [$t(58) = -2.14$, $p = 0.036$] and coverage [$t(58) = -2.22$, $p = 0.030$] of a rs-dFC state, which was implicated in bottom-up information processing. Increased dwell time was also correlated with a DI-induced improvement in Symbol Search ($r = 0.42$, $p = 0.02$). In subjects with higher residual CR, we observed a DI-induced increase in coverage [$t(58) = 2.11$, $p = 0.039$] of another rs-dFC state, which was implicated in top-down information processing. The study showed that DIs have a differential and behaviorally relevant effect on dynamic rs-dFC, but these benefits depend on the current CR level.

Keywords: cognitive reserve, dance intervention, dynamic resting-state functional connectivity, attention, bottom-up processing, top-down processing, dwell time, coverage

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INTRODUCTION

Some lifestyle factors are known to ameliorate the risk of cognitive decline and dementia. A study by Fratiglioni et al. (2004) proposed three factors that play this role, namely, social network, cognitive leisure, and physical activity. Dance interventions (DIs) represent a unique synergy of these three factors, which can affect a variety of age-related outcomes, including reducing the risk of falls (Rodrigues-Krause et al., 2016), decreasing depression (Marks, 2016), and influencing other fitness parameters associated with white matter integrity changes (Šejnoha Minsterová et al., 2020). Concerning cognition, research has shown that DIs have compelling benefits for the memory (Rehfeld et al., 2018), attention (Coubard et al., 2011), and psychosocial domains (Ehlers et al., 2017). A recent meta-analysis concluded that DIs deliver the strongest effects on global cognition and memory compared with not exercising or walking, but they do not have the same effect on inhibition or the task-switching aspects of executive function (Meng et al., 2020). In our previous study, we described improved figural fluency resulting from a 6-month DI as compared with the life-as-usual (LAU) condition (Kropáčová et al., 2019). Figural fluency evaluates the ability of executive functions to provide information about divergent reasoning, divided attention, planning, and mental flexibility (Johanidesová et al., 2014).

In terms of functional brain changes, exercise interventions generally led to increases in the resting-state functional connectivity (rs-FC) between the regions of the default mode network (DMN) (Li et al., 2014), between the DMN and motor networks (McGregor et al., 2018), and within the sensorimotor and frontoparietal networks; in the latter finding, exercise intervention was also associated with improved executive function (Voss et al., 2010). In a study by Rosano et al. (2010), physical activity treatment led to higher activations within the dorsolateral prefrontal, posterior parietal, and anterior cingulate (ACC) cortices of the executive control network during a digit symbol substitution test. As for the effects of DIs, the extent of our research showed that there is only one resting-state fMRI study that assessed the amplitude of low-frequency fluctuations (ALFFs) before and after a 3-month-long intervention in a group of 19 subjects with mild cognitive impairment (MCI). This study then found increased ALFFs in the frontotemporal, entorhinal, ACC, and parahippocampal cortices. Although the outcomes were not compared between the DI and control groups, they were associated with improvements in general cognition and memory, which was interpreted as DI-induced compensatory enhancement (Qi et al., 2019).

The existing body of literature reveals inconsistencies that may be due to underlying mediators of interindividual variability, particularly in aged subjects (Angevaren et al., 2008). It is plausible to hypothesize that the effect of interventions is moderated by individual levels of cognitive reserve (CR) (Kim et al., 2021). Cognitive reserve refers to the facilitation of flexibility and the efficiency of neural networks to compensate for aging and increasing brain pathology (Stern et al., 2018). It may also be responsible for the optimization and recruitment of brain networks (Conti et al., 2021). In line with this notion, a study by Lin et al. (2021) recently demonstrated that, in patients with MCI, high CR (as proxied by years of education) can alleviate the impact of brain hypometabolism on executive function. This is partially achieved by increasing both rs-FC in brain regions involved in the DMN and resting-state dynamic functional connectivity (rs-dFC) in the right frontoparietal network and DMN. A dynamic functional connectivity (dFC) approach to resting-state connectivity accounts for the presence of temporal variability in rs-FC (Allen et al., 2014). Subsequently, it adds relevant information to the depiction of the dynamic nature of the brain (Calhoun et al., 2014). Thus, the evaluation of rs-dFC may improve our understanding of CR mechanisms in the context of interventions; more specifically, it may increase our understanding of how CR is implicated in DI-induced brain plasticity changes.

Cognitive reserve is usually proxied by demographic variables associated with lifetime enrichment. However, this becomes less accurate with aging, particularly in those with more depleted compensatory mechanisms. Therefore, we estimated a residual CR index as the unexplained variance of cognitive composite predicted from brain status (Reed et al., 2010) to evaluate individual variability in DI-induced effects. In this study, we hypothesized that the level of residual CR would moderate DI-induced changes in the dynamics of distinct rs-dFC states and that these changes would be associated with specific DI-induced cognitive outcomes.

METHODS

Sample

A total of 99 community-dwelling, non-demented elderly (with MCI and healthy) subjects completed the study. All the subjects were over 60 years of age, without any medical, neurological, psychiatric, metabolic, or infectious disorders with an impact on cognition, such as major depression, drug and/or alcohol abuse, a history of traumatic brain injury, or any condition that would contraindicate DIs or MRI scanning. Subjects were randomized into a DI (N = 49) or a control (LAU) group (N = 50); see the study by Kropáčová et al. (2019) for the detailed enrollment and randomization processes. Then, each subject underwent a neuropsychological evaluation, MRI, and a physical fitness examination prior to the program and 6 months after the program completion. Demographic data included age, sex, education, clinical data (see section "Baseline Group Differences" and **Table 1**), and lifetime physical activities (**Supplementary Table 3**). Each subject signed the informed consent form in accordance with ethics codes and relevant regulations, and the study was then approved by the ethics committee of Masaryk University.

Dance Intervention

The intervention program was designed and supervised by experts at the Faculty of Sports Studies at Masaryk University. The intervention took 6 months for every 20 subjects and included three training units of 60 min per week. The duration of the study was 4 years. We aimed for a medium physical load intensity for each session, which included folk, country, African, Greek, and tango, each taught separately and developed over time into a final choreography. Only subjects who completed at least 60% of the DI program were included in the final cohort, resulting in an average compliance of 78.1%.

Neuropsychological Examination

Global cognition (MoCA), activities of daily living, and five cognitive domains, i.e., memory, attention, executive, visuospatial, and language, were evaluated with complex neuropsychological testing (**Supplementary Table 1**). Based on our previous results from the final cohort (Kropáčová et al., 2019), we focused on tests of the executive domain [Tower of Hanoi (Humes et al., 1997), Five-Point Test (Tucha et al., 2012)], the attention domain [Symbol Search and Digit Span (Wechsler, 1997)], and on global cognition (Nasreddine et al., 2005).

Physical Fitness Examination

Subjects were tested for physical parameters before and after the intervention (Šejnoha Minsterová et al., 2020). We evaluated body mass index, the 8-Foot Up-and-Go test, 30-Second Chair Stand test, 6-min Walk tests, and static (narrow and wide stance) and dynamic posture (standing up). The scores are compared in the **Supplementary Table 2**.

TABLE 1 | Mean differences in demographic, cognitive, and dynamic functional connectivity (dFC) outcomes between the dance intervention (DI) and life-as-usual (LAU) groups at the baseline level.

			n	Mean	SD	*t*	*P*
	Age	LAU	32	69.027	6.072	−0.149	n.s.
		DI	36	69.236	5.467		
	Education	LAU	32	15.00	2.995	0.300	n.s.
		DI	36	14.81	2.390		
	CR	LAU	29	−1.086	74.000	−0.096	n.s.
		DI	33	0.955	91.645		
	FA	LAU	32	0.430	0.019	−0.406	n.s
		DI	36	0.432	0.017		
	MoCA	LAU	32	25.81	2.945	−2.282	0.026
		DI	36	27.39	2.749		
FCS1	DT	LAU	32	5.026	3.235	−0.037	n.s.
		DI	36	5.059	4.101		
	C	LAU	32	0.228	0.084	0.027	n.s.
		DI	36	0.228	0.088		
FCS2	DT	LAU	32	4.621	2.859	−0.957	n.s.
		DI	36	5.405	3.769		
	C	LAU	32	0.278	0.117	0.647	n.s.
		DI	36	0.259	0.118		
FCS3	DT	LAU	32	4.742	3.516	0.770	n.s.
		DI	36	4.181	2.444		
	C	LAU	32	0.171	0.064	−1.710	n.s.
		DI	36	0.199	0.071		
FCS4	DT	LAU	32	4.992	2.809	0.572	n.s.
		DI	36	4.584	3.043		
	C	LAU	32	0.193	0.101	0.936	n.s.
		DI	36	0.172	0.083		
FCS5	DT	LAU	32	3.812	3.812	0.393	n.s.
		DI	36	3.228	3.228		
	C	LAU	32	0.130	0.118	−0.422	n.s.
		DI	36	0.142	0.113		

CR, residual index × 100; FA, mean fractional anisotropy of the white matter skeleton; education in years; DT, dwell time; C, coverage; MoCA, Montreal cognitive assessment test; DI, dance intervention group; LAU, life-as-usual group; n.s., non-significant; FCS, five dynamic resting brain states.

fMRI Examination and Preprocessing

The subjects were scanned using the 3T Siemens Prisma MRI scanner (Siemens Corp., Erlangen, Germany) by employing various sequences, including T1 structural data for vertex-based and volumetric analyses. Scanning was also done through diffusion tensor imaging for tract-based spatial statistics (Kropáčová et al., 2019; Šejnoha Minsterová et al., 2020). For the current study, we used r-s fMRI data by employing gradient-echo echo-planar imaging sequences (200 scans, 34 transversal slices, slice thickness = 3.5 mm, TR = 1,990 ms, TE = 35 ms, FA = 70°, FOV = 192 mm, matrix size 64 × 64). Resting-state fMRI data were preprocessed using the SPM 12 toolbox (Wellcome Department of Imaging Neuroscience, UCL, UK) and Matlab 2014b (The MathWorks, Inc, Natick, United States). Preprocessing included realignment and unwarping, normalization into standard anatomical space (MNI), and spatial smoothing with 5 mm full width at half maximum (FWHM). More details on dealing with motion artifacts can be found in the **Supplementary Material** (page 1).

Independent Component Analysis

The data from the subjects who had fMRI data that were of sufficient quality in both sessions were entered into a single group spatial independent component analysis (gsICA) (Calhoun et al., 2001) implemented in the Matlab-based toolbox, group ICA of fMRI Toolbox (GIFT) (TReNDS, GA, United States). The Infomax algorithm and ICASSO framework (Himberg et al., 2004) were then used to derive the maximally spatially group-specific independent components, while the group ICA (GICA) algorithm was used to render dataset-specific spatial maps and time-series. More details on ICA preprocessing can be found in the **Supplementary Material** (page 1).

Dynamic Functional Network Connectivity

All 20 components were identified using the ICA. We visually inspected the spatial maps of the components and selected those representing functional networks. The sliding window correlation, i.e., Pearson's approach (Chang et al., 2013; Shakil et al., 2016), between the temporal-series of nine selected independent components (ICs) were calculated. For each subject and condition, a window length of 60 s and 90% overlap formed a series of 56 correlation matrices 9 × 9.

Furthermore, *k*-means clustering was used to find recurring functional network states (Allen et al., 2018). Network state vectors, composed as the assignment of the correlation matrix of each subject in a time series to the nearest cluster by the *k*-means algorithm, were used to extract the parameters of network state dynamics (Díez-Cirarda et al., 2018). Parameters include (1) dwell time or mean duration, i.e., mean time of stay in a specific state and (2) time coverage, i.e., the percentage of data coverage by a specific state. For more details on the correlation matrices and clustering algorithm, see **Supplementary Material** (page 1).

Residual CR

To obtain the residual CR proxy that reflects the current levels of pathological burden and cognitive performance, we calculated the residual difference between the observed memory performance and the prediction by (1) the hippocampal-to-intracranial volume ratio (Kropáčová et al., 2019), (2) fractional anisotropy (FA) of the white matter skeleton (Šejnoha Minsterová et al., 2020), and (3) age as a major risk factor for cognitive decline. Memory performance was selected to represent one of the most common domains to decline in healthy or pathological aging. The composite was calculated as the z-score of the Taylor figure (Warrington and Taylor, 1973) and Logical memory (Wechsler, 1997) (both immediate and delayed recall; see **Supplementary Table 1**). Intracranial volume as a denominator controlled for head size. The residual CR index was a continuous variable in which higher values indicate more reserve, i.e., capacity to compensate.

Statistical Analyses

Between-group differences at baseline in dwell time and coverage of dFC states and demographics were compared using t-tests for continuous variables, chi-square tests for categorical variables, and Mann–Whitney U tests for mean ranks.

Linear mixed models (LMMs) were computed to assess the interaction effect between time*group*CR on the dwell time and coverage of the rs-dFC states. These LMMs included (1) random intercepts to account for variability across individuals, (2) time as a repeated measure with an unstructured covariance type to account for high correlations between outcome variables measured at two time points, and (3) no random factors, as they did not improve the fit of models. The first-level, basic LMM included only fixed factors with the main effects of time (dichotomous), cognitive reserve (continuous variable), and group (dichotomous, DI vs. LAU). Age and sex were selected as covariates and included as main effects. The second-level LMMs were run with the same main effects and interactions of time*group and time*group*CR. The fit of the models with significant interaction effects was compared with the basic model using the X^2-change of maximum likelihood estimation (–2 LL).

To probe significant three-way interactions from the LMMs, moderation analyses were computed to test the effect of CR (moderator variable) on the relationship between the program and the change in dwell time and/or coverage of the rs-dFC states. Using the Johnson–Neyman output made modeling the effects of different levels of the CR moderator possible, consequently simplifying the interpretation of interactions based on zones of significance without necessitating multiple tests of single main effects. The HC3 option (Davidson-MacKinnon) was also selected for its heteroscedasticity-consistent standard errors, while only the continuous variables that predicted the outcome were centered.

Finally, we conducted exploratory two-tailed partial correlations for the purposes of interpretation by accounting for CR between changes in the rs-dFC parameters and cognitive tests of interest in the DI group. The rs-dFC states that significantly changed as a result of the time*group*CR interaction were the only one that were correlated, as we were specifically interested in the unique relationship between the rs-dFC states and cognitive tests. Furthermore, changes in variables of interest for moderation and correlations were computed as timepoint_2 (a follow-up) − timepoint_1 (baseline).

RESULTS

Subjects

From the original cohort of 120 subjects, we excluded 21 who did not complete at least 60% of the DI. More subjects were later excluded due to insufficient fMRI data quality. The final dataset was comprised of 36 DI and 32 LAU subjects; a total of $68 \times 2 = 136$ datasets were entered into further analyses. For the demographic, clinical, and MRI data, see **Table 1**.

Independent Component Analysis

In this study, we selected nine components that represented functional networks: the cerebellum, DMN, visual network (VN), right and left frontoparietal network (r/l-FPN), language network (LN), salience (insulo-opercular) network (SAL), frontoparietal control network (FPCN), and sensorimotor network (SMN) (**Figure 1A**).

Dynamic Functional Connectivity States

Altogether, five rs-dFC states (FCS1–5) were identified (**Figure 1B**). For the baseline differences in coverage and dwell time in the DI and LAU groups, see **Table 1**.

The first functional connectivity state (FCS1) was characterized by sparsely connected networks, where the DMN significantly correlated with both salience and visual networks, thus suggesting bottom-up processing and readiness to salient stimuli. A sparsely connected FCS2 state was characterized by overall negative correlations, particularly between the DMN and SAL, suggesting a disconnected resting state. The FCS3 state was characterized by anticorrelations between task-positive and task-negative networks and resembled a typical "mind wandering" resting state. In contrast to the three FCSs, the last two identified states were highly interconnected with FCS4, suggesting both top-down and bottom-up processing readiness. Additionally, FCS5 was partially inverse to FCS1 but displayed disconnection between the DMN and SAL, thus resembling a resting state.

Baseline Group Differences

The two experimental groups were equivalent in terms of age, education, residual CR, and parameters of the identified FCSs at the baseline (see **Table 1**). Similarly, the proportion of subjects with MCI ($n = 21$) [$X^2(1) = 1.24$; $p = 0.27$] and male-to-female ratio [15:51; $X^2(1) = 3.02$; $p = 0.082$] did not significantly differ between the DI and the LAU groups. The baseline comparisons of the tests of interest from the attention and executive domains between DI and LAU also did not differ ($p > 0.05$, data not shown). There were no between-group differences in baseline fitness parameters (**Supplementary Table 2**) or in lifetime engagement in aerobic ($U = 540$, $Z = -0.23$, $p = 0.82$) and anaerobic activities ($U = 471$, $Z = -1.22$, $p = 0.22$) (details reported in **Supplementary Table 3**).

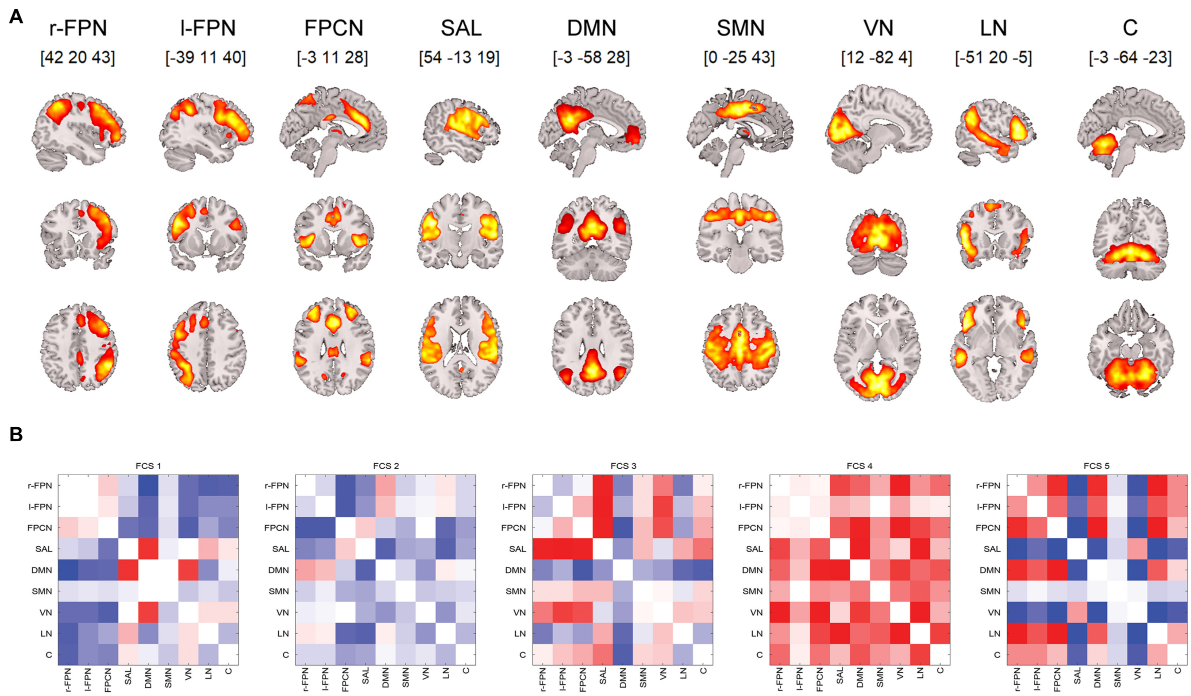

FIGURE 1 | (A) Nine ICA components analyzed for the resting-state dynamic functional connectivity. **(B)** Five identified rs-dFC states (1–5 from the left). Each matrix depicts mutual correlations between each component identified using the ICA. Dark blue suggests a high negative correlation, and dark red suggests a high positive correlation. Note: rs-dFC, resting state dynamic functional connectivity states; r/l-FPN, right/left frontoparietal network; FPCN, frontoparietal control network; SAL, salience (insulo-opercular) network; DMN, default-mode network; SMN, sensorimotor network; VN, visual network; LN, language network; C, cerebellum.

Analyses of rs-dFC States

There were no significant interactions in the FCS2, FCS3 and FCS5 predictions. For a detailed report of the LMM fixed effects in all five states, see **Supplementary Table 4**.

FCS1 State

The dwell time of the FCS1 state was significantly predicted by a model with the time*group*CR interaction term, with a significantly better fit [$X^2(3) = 11.46$, $p < 0.01$] than the basic model with only the main effects and covariates −2 LL(9) = 675.908, and also in comparison to a model with the same main effects and the simple time*group interaction term [$X^2(2) = 10.56$, $p < 0.01$]. Only the interaction between time*group*CR significantly predicted the change in the dwell time of FCS1 $F(3,73) = 4.17$, $p = 0.009$ (see **Supplementary Table 4**), but not the main effects of predictors and covariates. The follow-up Johnson–Neyman technique to determine zones of significance revealed that DIs positively predicted FCS1 dwell time increases at lower values of residual CR [from approximately −0.5 SD ($t = 2.01$, $p = 0.05$) to the lowest CR levels ($t = 2.31$, $p = 0.024$)] (**Figure 2**).

Similarly, the coverage of FCS1 was significantly predicted by a model with the time*group*CR interaction, which was a significantly better fit [$X^2(3) = 8.72$, $p < 0.05$] than both the basic model −2 LL(9) = −240.386 and a model with the simple time*group interaction term [$X^2(2) = 8.7$, $p < 0.05$]. In this model, only the interaction between time*group*CR significantly predicted the coverage of FCS1 $F(3,70) = 3.13$, $p = 0.031$ (see **Supplementary Table 4**), whereas the main effects of the predictors and covariates were not significant. The follow-up Johnson–Neyman technique to determine zones of significance revealed that DI had a positive significant effect on the increased coverage of FCS1 at lower values of residual CR [from approximately −1 SD ($t = 2.01$, $p = 0.05$) to the lowest CR levels ($t = 2.32$, $p = 0.024$)].

In other words, both the dwell time and coverage change of the FCS1 state were moderated by CR and increased after the DI in subjects with low residual CR.

According to the partial correlation results in the DI group, the increase in the dwell time of FCS1 was associated with improvement in the Symbol Search task ($r = 0.41$, $p = 0.023$).

FCS4 State

The linear mixed models of the dwell time of FCS4 did not reveal any significant predictors of change. However, the coverage was significantly predicted by a model with the time*group*CR interaction, which was a significantly better fit [$X^2(2) = 7.06$, $p < 0.05$] than a basic model with only the main effects of fixed factors and covariates −2 LL(9) = −256.221, but not in comparison with a model with the same main effects and simple time*group interaction term [$X^2(1) = 3.57$, $p = 0.059$] (**Supplementary Table 4**). The time*group*CR interaction term had the greatest effect $F(3,72) = 2.61$, $p = 0.058$. When proceeding with a simpler moderation analysis, Johnson–Neyman zones of significance

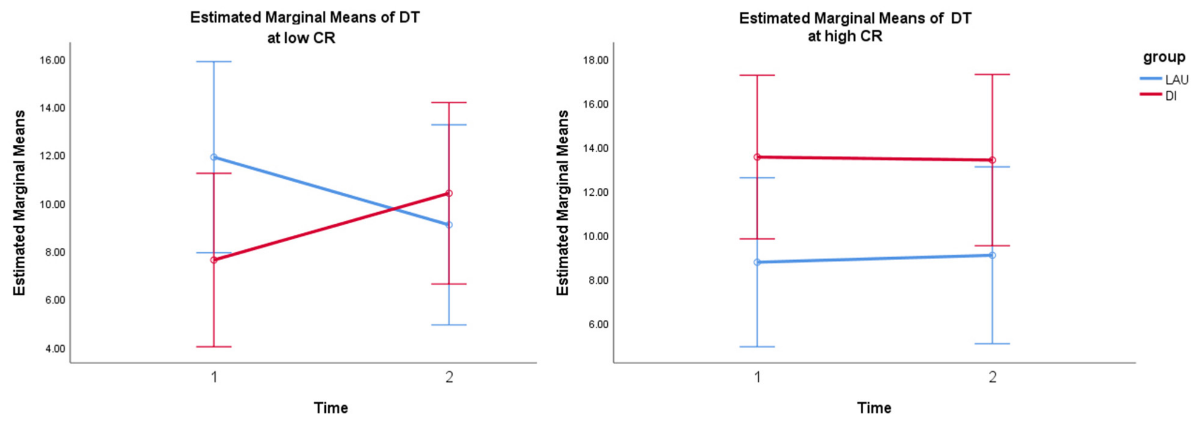

FIGURE 2 | Simple slope analysis of time*group interaction in low vs. high CR (based on median-split grouping) depicts significant interaction at lower values of CR. Error bars: 95% CI. Note: DT, dwell time; CR, cognitive reserve; LAU, life-as-usual; DI, dance intervention.

supported the abovementioned interaction effect [$t(58) = 2.11$, $p = 0.039$]. Furthermore, DIs also positively predicted FCS4 coverage changes from moderate ($t = 2.01$, $p = 0.05$) to the highest levels of residual CR ($t = 2.58$, $p = 0.012$).

In other words, the coverage change of the FCS4 state was moderated by CR and increased after the DI in subjects with moderate to the highest residual CR levels.

Partial correlations in the DI group did not yield any significant results for the association between FCS4 and cognitive changes.

DISCUSSION

The novelty of our study stems from the evaluation of the temporal dynamics of inter-network connectivity between several large-scale brain networks at the baseline and following a 6-month DI in non-demented (HC and MCI) elderly as compared with a control condition (LAU). Cognitive reserve is involved in the optimal recruitment of brain networks, which is important to maintain cognitive performance and compensate for cognitive decline. By implementing the individual residual levels of CR that account for brain pathology and memory performance, we were able to evaluate how current CR capacity can moderate the effects of a comprehensive DI program on the dwell time and coverage of several brain rs-dFC states.

This study reported two main findings. The first finding was related to the temporal dynamics of the sparsely connected rs-dFC state 1, which was characterized by a significant correlation between the SAL and the DMN. The DMN in turn positively correlated with the VN, whereas the FPCN was significantly anticorrelated with both the SAL and DMN and the cerebellar, VN, and language networks. The dwell time and coverage of this state increased in the DI group as compared with the LAU group, but only in people with low residual CR, invariantly of age and sex. Increased engagement of the insula and decreased involvement of the FPCN in individuals with low CR were previously shown in a study by Huang et al. (2019) on depressed elderly subjects during an emotional interference task. It has been proposed that the insula, as part of the SAL, is involved in detecting and filtering salient stimuli, subsequently guiding behavior by engaging in the dynamic coordination of large-scale networks (Seeley et al., 2007; Uddin, 2015), and switching between task-negative (DMN) and task-positive (FPN) networks (Menon and Uddin, 2010). Other task-based fMRI studies have shown the role of the ACC and the insula in experiencing thirst, hunger, pain, embarrassment, and other emotions (Craig, 2002; Critchley, 2005). Therefore, the results of this study suggested that, by prolonging the coverage and dwell time of this particular dynamic state, the DI enhanced readiness to the bottom-up processing of new relevant stimuli in low-CR individuals by drawing attention to input signals from the internal environment (SAL and DMN) and the external environment (VN).

The increase in dwell time of the rs-dFC state was accompanied by improvements in the Symbol Search score, an established measure of psychomotor and visuomotor processing speed, visual discrimination, and attention. This is clinically relevant because the test has a strong negative relationship with age due to declining processing speed (Joy and Fein, 2001). The finding that Symbol Search performance was more readily improved with bottom-up processing accords with the notion that low-CR individuals rely on less effective bottom-up information processing, probably due to their already depleted top-down processing (Steffener and Stern, 2012). Interestingly, the dwell time and coverage of state 1 in high-CR subjects remained stable in time in both the DI and LAU groups.

The second finding indicated that subjects with high residual CR displayed DI-induced increases in the coverage of the highly interconnected state 4, in which the SAL was positively correlated with the DMN and the DMN also positively correlated with the FPCN. Thus, FCS4 may represent increased readiness for top-down information processing in high-CR individuals, which was enhanced by the DI. Other authors have supported the notion that the cognitive functioning in high-CR individuals employs more prefrontal and frontoparietal networks, e.g., in Alzheimer's disease (Colangeli et al., 2016), and engages in attentional, executive (Decety and Lamm, 2006), and complex cognitive operations (Song et al., 2017). In the FCS1, the DMN was also correlated with the VN, although less strongly than with the FPCN, which suggested readiness for bottom-up processing in addition to top-down cognitive control. However, the changes in the dynamic state 4 in high-CR individuals did not correlate with changes in cognitive tests. Such a result may be a consequence of the already optimized cognitive functioning among high-CR subjects and/or of the lower sensitivity of the administered tests.

Cognitive reserve is defined as an active process in which flexible and efficient neural networks compensate for age- or disease-related neurocognitive declines (Stern et al., 2018). The current results shed light on how CR moderates intervention-induced rs-dFC changes that underpin optimized cognitive processing in non-demented elderly subjects. Specifically, we observed that the DI-induced benefits in cognitive processing were dependent on the CR level and linked to distinct and differential neural mechanisms as assessed by rs-dFC. In low-CR subjects, the DI enhanced bottom-up processing, while in high-CR individuals, the DI particularly affected top-down processing. These findings could aid in individualization and evaluation in future intervention studies, as they underscore the importance of monitoring the individual capacity for brain plasticity changes and network optimization due to interventions.

This current study has its limitations, which the authors recognize. First, we used a non-active "life-as-usual" control group; thus, we were unable to control for other significant factors such as the effect of socialization. Second, the subjects with MCI could not be analyzed separately due to low representation. Future studies may also confirm our findings in patients with MCI and dementia.

Dynamic resting-state functional connectivity offers a new approach to studying functional connectivity on time-varying frameworks of coupling among brain networks. Therefore, it allows for the representation of multiple brain states (Allen et al., 2014). Previous studies utilizing this approach linked CR in young professional chess players to enhanced global dynamic fluidity and a higher number of occupied states (Premi et al., 2020). Thus, this study employed rs-FC and brain state dynamics to study controlled pre-to-post intervention effects in the context of age-related CR depletion.

The results of this study clearly supported our hypothesis that individual differences in CR moderate the brain plasticity outcomes of an intervention program. Specifically, it was found that the changes in rs-dFC observed in the DI group subjects were CR-specific and behaviorally relevant. They reflected enhanced bottom-up cognitive processing in the low-CR subjects, which was probably due to the depleted capacity of the frontoparietal networks, and enhanced top-down information processing in those with high residual CR. The study provided the first pieces of evidence for individual variability in DI-induced rs-dFC changes in aging brains and offered new insight into the role of DIs in enhancing brain function in aged non-demented subjects.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

KM, IR, MP, PŠ, PV, AS, and RG: study conception and design. KM, MP, PŠ, PV, AS, and RG: data collection. KM, ML, RM, and IR: analysis and interpretation of results. KM: draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.724094/full#supplementary-material

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Dance Intervention Impact on Brain Plasticity: A Randomized 6-Month fMRI Study in Non-expert Older Adults

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Background: Dance is a complex activity combining physical exercise with cognitive, social, and artistic stimulation.

Objectives: We aimed to assess the effects of dance intervention (DI) on intra and inter-network resting-state functional connectivity (rs-FC) and its association to cognitive changes in a group of non-demented elderly participants.

Methods: Participants were randomly assigned into two groups: DI and life as usual (LAU). Six-month-long DI consisted of supervised 60 min lessons three times per week. Resting-state fMRI data were processed using independent component analysis to evaluate the intra and inter-network connectivity of large-scale brain networks. Interaction between group (DI, LAU) and visit (baseline, follow-up) was assessed using ANOVA, and DI-induced changes in rs-FC were correlated with cognitive outcomes.

Results: Data were analyzed in 68 participants (DI; $n = 36$ and LAU; $n = 32$). A significant behavioral effect was found in the attention domain, with Z scores increasing in the DI group and decreasing in the LAU group ($p = 0.017$). The DI as compared to LAU led to a significant rs-FC increase of the default mode network (DMN) and specific inter-network pairings, including insulo-opercular and right frontoparietal/frontoparietal control networks ($p = 0.019$ and $p = 0.023$), visual and language/DMN networks ($p = 0.012$ and $p = 0.015$), and cerebellar and visual/language networks ($p = 0.015$ and $p = 0.003$). The crosstalk of the insulo-opercular and right frontoparietal networks were associated with attention/executive domain Z-scores ($R = 0.401$, $p = 0.015$, and $R = 0.412$, $p = 0.012$).

Conclusion: The DI led to intervention-specific complex brain plasticity changes that were of cognitive relevance.

Keywords: dance intervention, resting state fMRI, independent component analysis, intra-network connectivity, attention, cognitive

INTRODUCTION

Dance is a complex activity combining physical exercise with cognitive, social, and artistic stimulation (Burzynska et al., 2017). While the beneficial effect of dance intervention (DI) programs on physical fitness have been repeatedly proven, papers assessing the effects of DI on cognition have mixed results (Alpert et al., 2009; Coubard, 2011; Kim et al., 2011; Kattenstroth et al., 2013; Müller et al., 2017; Rehfeld et al., 2017, 2018; Brustio et al., 2018; Qi et al., 2018b). The effects of dance intervention on brain plasticity include various structural changes, such as an increase in gray matter volume (left hippocampus, left dentate gyrus, left precentral gyrus, etc.) as well as an increase in white matter integrity (fornix, corpus callosum), for a full review please see Teixeira-Machado et al. (2019). These findings are in concordance with our recent works, where 6-month-long DI as compared to life activities as usual (LAU) and resulted in significant improvement in a Five Point Test (FPT) which evaluated attention and executive functions (Kropacova et al., 2019), and in increases of cortical thickness of the right lateral occipitotemporal cortex (Rektorova et al., 2020) implicated in learning new skilled movements (Gatti et al., 2017). Physical fitness also significantly improved due to the 6-month DI, which was linked to changes in diffusion tensor imagining measures in the whole white matter skeleton and in the corticospinal tract and the superior longitudinal fascicle, which are engaged in motor learning and movement execution, as well as in spatial attention, manipulation of mental representations, and speech comprehension (Sejnoha Minsterova et al., 2020).

Brain connectivity changes following aerobic exercise of various types and intensities were studied by several authors. Increase of resting-state functional connectivity (rsFC) following aerobic exercise was often reported in the default mode network (DMN) and hippocampus and parahippocampal gyrus regions (Burdette et al., 2010; Rosano et al., 2010; Voss et al., 2010; Leavitt et al., 2014; Boraxbekk et al., 2016; Tozzi et al., 2016; Chirles et al., 2017; McGregor et al., 2018; Ikuta et al., 2019). A 6-month-long aerobic exercise intervention in MCI patients led to increased rsFC of the prefrontal cortex (Hugenschmidt et al., 2017), similarly, the aerobic exercise intervention of the same duration led to increased rsFC in the prefrontal cortex, as well as superior parietal gyrus/precuneus in older overweight adults compared to the control group (Prehn et al., 2019). Not only regular but also a single session of moderate aerobic exercise resulted in increased FC in the sensorimotor areas (pre/post central gyri, thalamus and secondary somatosensory area) of healthy young adults (Rajab et al., 2014). Similarly, a 30-min long exercise bout was reported to increase rsFC in the right fronto parietal network (rFPN), sensorimotor network (SMN), and right affect and reward and network (ARN) in male athletes (Schmitt et al., 2019). However, some studies reported limited or no effect of aerobic exercise on rsFC (Flodin et al., 2017; Cui et al., 2019).

Although dance, unlike simple aerobic activity, involves learning and attention, emotions, coordination and balance, acoustic stimulation and social interaction (Kshtriya et al., 2015) only one study to date (Qi et al., 2018b) used rs-fMRI to examine the effect of the intervention on FC. The results of this pilot 3-month-long aerobic dance intervention in older adults with MCI showed an increase in brain spontaneous activity (analysis of the amplitude of low-frequency fluctuations) in bilateral fronto temporal, hippocampal, entorhinal and anterior cingulate cortices, compared to baseline (Qi et al., 2018b).

Based on this promising preliminary finding, we decided to use fMRI and a data-driven independent componential analysis (ICA) approaches with a primary objective to assess the effect of DI on rsFC in a mixed group of healthy elderly with or without MCI but no dementia. We hypothesized that DI-induced task-specific changes in both within-network and between-network rsFC in the DI group compared to the LAU group. Our secondary objective was to evaluate the association between the DI-induced changes in rsFC and cognitive performance. Based on our previous results (Kropacova et al., 2019; Rektorova et al., 2020), we particularly focused on DI-induced changes in attention and executive function domains. We hypothesized that DI-induced brain plasticity changes will be linked with our cognitive outcomes of interest.

METHODS

Study Participants and Intervention

Volunteers older than 60 were recruited using several sources, such as free advertising in community centers (senior centers, libraries), University of the Third Age courses, and in public media such as local newspapers and leaflets, etc. The exclusion criteria included serious brain injury, major psychiatric disorder or central nervous system disease, other serious neurological, orthopedic, oncological or internal disease disabling participation in the dance-exercise intervention, as well as any contraindications of MRI scans as followed in clinical practice. The abuse of alcohol, other addictive substances and smoking were other exclusion criteria. Volunteers practizing sport activities more frequently or at a more demanding level than the dance exercise intervention were not included in the study.

Participants were randomly assigned into two groups in a 1:1 ratio: DI (dance intervention) and LAU (life as usual) using the opaque envelope method. The study sample was estimated based on pilot data analysis, when a mean change of 0.5 points was observed in the five-point test score (Kropacova et al., 2019). Considering the type 1 error probability α of 0.05 and expecting the test power β of 0.8, and also considering a dropout rate of 25%, the minimum number of participants in one group was calculated to be 42. It should be noted that in the presented paper, the five point test is not included in the analysis. Participants who were eventually included in the analysis were those who completed the study protocol (at least 66.6% attendance of dance-exercise intervention in DI group, 2 fMRI scans, 2 detailed neuropsychological examinations before and after the intervention and physical fitness assessment).

Participants included in the DI group followed a 6-month-long dance exercise course taking place three times a week, the duration of a single lesson was 60 min and it took place at the Faculty of Sports Studies, Masaryk University in Brno. The dance exercise training was prepared and led by professionals from the faculty. The intervention included various dance types, e.g., Irish country, African, and Greek, etc., which were combined into a final choreography and performed at medium physical load intensity three times per week (Kropacova et al., 2019; Rektorova et al., 2020). Participants in the LAU group led normal lives.

Neuropsychological Examination

The complex neuropsychological testing evaluated global cognitive functions (Montreal Cognitive Assessment—MOCA) and five domains: memory, attention, executive functions, visuospatial functions, and language. Subjects who scored below −1.5 SD in two tests in at least one cognitive domain compared to normative data were categorized as having MCI. Activities of daily living and depressive symptoms were also evaluated to exclude subjects with dementia or depression (Kropacova et al., 2019). For further details, see the **Supplementary Material**.

MRI Data Acquisition and Preprocessing

All subjects were scanned in 3T Siemens Prisma MR scanner (Siemens Corp., Erlangen, Germany) at the Central European Institute of Technology (CEITEC), Masaryk University in Brno, using the following sequences: magnetization-prepared rapid gradient-echo (MPRAGE) high-resolution T1-weighted images (240 sagittal slices, slice thickness = 1 mm, TR = 2,300 ms, TE = 2.34 ms, FA = 8°, FOV = 224 mm, matrix size 224 × 224) and gradient-echo echo-planar imaging sequence for resting state fMRI (200 images, 34 transversal slices, slice thickness = 3.5 mm, TR = 1,990 ms, TE = 35 ms, FA = 70°, FOV = 192 mm, matrix size 64 × 64).

The resting state fMRI data were preprocessed using the SPM 12 toolbox and Matlab 2014b. Preprocessing included realignment and unwarping, normalization into standard anatomical space (MNI) and spatial smoothing with 5 mm FWHM. The level of motion was thoroughly checked in terms of frame-wise displacement (FD) (Power et al., 2012). No FD was higher than 3 mm and scans that displayed FD > 0.75 mm were scrubbed (Power et al., 2012). No more than 2.5% of subject scans were removed. Moreover, the six movement regressors (obtained during realignment and unwarping), FD and extracted signals from white matter and cerebrospinal fluid were regressed out of the data in subsequent analysis. Assessment of functional connectivity changes using independent component analysis (ICA).

Regarding the rs-fMRI data analyses, we utilized the data-driven approach using independent component analysis (ICA) methods. The intra-network and inter-network connectivity (intra-NC and inter-NC) of major large-scale brain networks were also evaluated, see the details below.

The data from all subjects ($n = 68$, 36 DI and 32 LAU) and both sessions (a total of 136 fMRI datasets) were entered into single group spatial Independent Component Analysis (gsICA) (Calhoun et al., 2001) implemented in the GIFT toolbox running under MATLAB. At first, each dataset was further preprocessed to remove the mean per each voxel time series and reduced by Principal Component Analysis (PCA) with the number of components set to the maximum Minimum Description Length (MDL) estimate for all datasets (Li et al., 2007). Then, a second PCA reduction was applied to all PCA components from all datasets with the number of components set to median over MDL estimates. Finally, the Infomax algorithm and ICASSO framework (Himberg et al., 2004) was used to derive maximally spatially group-specific independent components and the GICA algorithm was used to render dataset-specific spatial maps and time-series (20 runs with random initialization, minimal cluster size 16, maximal cluster size 24). We visually inspected spatial maps of the resulting components and those that represent functional networks were used for ensuing intra-NC analysis and the respective back-reconstructed time-series were used to evaluate inter-NC connectivity.

Experimental Design and Statistical Analysis

The study was completed between September 2015 and June 2018 and was divided into three parts. In September and October, the participants underwent neuropsychological and physical assessment and fMRI data were acquired, the data acquisition took place at CEITEC, Masaryk University, and at Faculty of Sports Studies, Masaryk University in Brno.

The intervention itself took place from November to April. In May and June, the re-assessments were performed in both groups.

Two sample t-test and Fischer Exact tests were used to compare the demographic data and cognitive performance between the two groups before the intervention. The effect of the intervention on cognitive performance was tested using ANOVA with three factors ("subject," "group"—DI or LAU, and "visit"—before and after intervention), with age, sex and education as covariates.

Intra-Network Connectivity Analysis

For intra-network connectivity analysis, the groups at baseline were first compared using ANOVA, with a group (DI or LAU) as a factor. Then, the group differences between "before" and "after" intervention were compared using ANOVA, with three factors: group (DI or LAU), subject and visit (before, after), and an interaction group x visit. Both models included three nuisance covariates (age, gender and years of education). Both models were analyzed for each selected component and the analysis included only voxels significantly active within the given network. Altogether, 20% of voxels with the highest absolute value were included in the analysis. The significance level was set to $p < 0.05$ FWE corrected (cluster level, initial cut $p = 0.001$ uncorrected) corrected for multiple comparisons using Random Field Theory (Nichols and Hayasaka, 2003).

Inter-Network Connectivity Analysis

For inter-network connectivity analysis, subject-specific static functional connectivity between all pairs of selected ICA components (correlation coefficient) was calculated based on the components' time series. The resulting correlation coefficients were transformed into Z-scores using Fisher Z-transform. Again, the groups at baseline were first compared using ANOVA with a single factor—group (DI or LAU). The group differences between "before" and "after" intervention were compared using ANOVA, with three factors: group (DI or LAU), subject and visit (before, after) and an interaction group x visit. The main effect of all three factors and interaction of group (DI or LAU) and "visit" (before, after) was modeled. For both models, three covariates were included (age, gender and years of education). Both models were calculated for each connection (altogether 36 connections, 9 components between each other). The significance level was set to $p < 0.05$ with Bonferroni corrections on two contrasts ($p < 0.025$, 2 × main effect of a factor "group" (DI or LAU) or 2 × interaction "group" X "visit").

All ANOVAs with three factors included the "subject" factor, which modeled an effect of repeated measures. In case of any significant group vs. visit results, we also performed a correlation between changes in the rs-FC and cognitive domain z-scores in the DI group. The connectivity changes were corrected for age, sex and education.

RESULTS

Participant Characteristics

Altogether, 147 subjects were recruited, 120 were included in the study after reviewing the inclusion and exclusion criteria. Eleven participants included in the DI group did not meet the criterion of the minimum attendance (66.6%), those whose attendance was lower than 10% were offered to be moved to the LAU group (6 participants). Eleven participants of the LAU group were lost to follow-up.

In the present study, we analyzed data from 68 subjects from the final cohort who had good quality fMRI data, 36 DI participants and 32 LAU participants. There were no differences in age, education and MOCA scores (two sample t-test, $p < 0.05$) and men/women ratio (Fischer Exact test, chi square = 1.24, $p = 0.265$) between the two groups. A significant difference between the groups was found for gender distribution (Fischer Exact test, chi square = 3.95, $p = 0.047$). Both DI and LAU were heterogeneous groups consisting of both healthy controls (HC) and subjects with mild cognitive impairment (MCI). There was no difference between the DI and LAU groups in healthy seniors (HS) and MCI ratio.

Cognitive Outcomes

The results of cognitive examinations are summarized in **Supplementary Table 1**. There were no differences in cognitive domain Z scores between the groups before the intervention (two sample t-test, $p < 0.05$) (see **Table 1**).

The interaction of factors "group" and "visit" was significant for the attention domain, with Z scores increasing in the DI group and decreasing in the LAU group ($F = 6.00$, $p = 0.017$) (see **Supplementary Figure 2**).

TABLE 1 | Baseline demographic and cognitive examination data.

	DI (N = 36)	LAU (N = 32)	p-value
Age (years)	69.2/5.47	69.0/6.08	0.878
Gender (M/F)	5/31	11/21	0.047
Control/MCI	27/9	20/12	0.265
Education (years)	14.8/2.31	15.0/3.02	0.697
MOCA	27.2/2.81	25.9/2.93	0.069
Memory (Z score)	1.12/1.03	1.12/0.84	0.997
Attention (Z score)	0.11/0.57	0.05/0.76	0.738
Executive (Z score)	–0.36/0.64	–0.32/0.65	0.795
Visuospatial (Z score)	0.30/0.56	0.40/0.53	0.727
Language (Z score)	0.39/0.47	0.40/0.45	0.938

Independent Componential Analysis Resting-State fMRI Results

Altogether 20 components were identified using the Independent Component Analysis. We visually inspected the spatial maps of the components and for further analysis of inter and intra-network connectivity, we selected those representing functional networks—cerebellum, DMN, visual network, right and left frontoparietal network, language network, salience (insulo-opercular) network, frontoparietal control network and sensory-motor network (see **Supplementary Figure 1**).

Dance Intervention-Induced Changes in Intra-Network Connectivity

There were no significant differences in intra-network connectivities between DI and LAU groups at baseline. We observed significant interaction "group" x "visit" for the DMN. Based on extracted average values, the connectivity increases in the DI group and decreases in the LAU group (ANOVA, $p = 0.048$ FWE). The rs-FC in the precuneus (MNI coordinate −9, −58, 25) increased in the DI group and it decreased in the LAU group ($p = 0.048$) (see **Supplementary Figure 3**).

Dance Intervention -Induced Changes in Inter-Network Connectivity

There were three significant differences in inter-NC between the DI and LAU groups before the intervention, in all three the connectivity was higher in the LAU group compared to the DI group (cerebellum –visual network—$p = 0.0088$, cerebellum—language—$p = 0.01$, language—sensory-motor network—$p = 0.0218$).

We found six significant results for the group vs. visit interaction. Based on the extracted average values, the inter-NC increased in the DI group (five results) and decreased in the LAU group (one result). The inter-NC between the networks decreased significantly more in LAU than in the DI group (see **Table 2** and **Figure 1**). Briefly, DI, when compared to LAU, induced increases in the crosstalk between the insulo-opercular and right frontoparietal/frontoparietal control networks ($p = 0.019$ and $p = 0.023$), visual and language/DMN networks ($p = 0.012$ and $p = 0.015$), and cerebellar and visual/language networks ($p = 0.015$ and $p = 0.003$).

TABLE 2 | The significant results in inter-NC connectivity between the pairs of networks.

Networks	*P*-value
Cerebellum vs. visual network	0.0147
Default mode network vs. visual network	0.0149
Cerebellum vs. language network	0.003
Visual vs. language network	0.0119
Right frontoparietal vs. salience network	0.0186
Salience network vs. frontoparietal control network	0.023

Association Between Resting-State Functional Connectivity Changes and Cognitive Outcomes of Interest

The DI-induced changes in inter-NC between the right frontoparietal network and salience network significantly correlated with changes in attention domain z-scores ($R = 0.402$, $p = 0.015$) and executive function domains ($R = 0.412$, $p = 0.012$) in the DI group (see **Figures 2A–C**).

DISCUSSION

The significant behavioral effect of DI was found in the attention domain, which is in concordance with previous research (Diamond, 2015; Xiong et al., 2021) and our other research, which was performed in the same final cohort with a larger sample size (Kropacova et al., 2019). The current cohort remains smaller due to discarding data from participants with motion artifacts during fMRI scanning.

Our main goal was to assess brain rsFC changes that reflect DI-induced ability to enhance the recruitment of relevant cognitive large-scale brain networks and/or communication between them. For this purpose, we analyzed rsFC changes within specific networks as well as those of individual network pairings. We observed group vs. visit interaction for the DMN intra-network connectivity which increased in the DI group and decreased in the LAU group. DMN is a main resting state cognitive network with high degrees of functional connectivity (Greicius et al., 2003). Reduced rsFC within DMN has been described in both normal and pathological aging (such as in MCI or Alzheimer's disease), with DMN having a strong correlation with cognitive processes (Agosta et al., 2012; Krajcovicova et al., 2014; Vidal-PiÃ±eiro et al., 2014; La et al., 2015; Qi et al., 2018a; Zonneveld et al., 2019). The positive effect of exercise, both short and long-term, on the plasticity of DMN, has already been described by several studies (Boraxbekk et al., 2016; Li et al., 2017; McGregor et al., 2018).

We found more significant results for the DI-induced rs-FC enhancement of the inter-network crosstalk than of the intra-network connectivity. This finding may relate to the fact that aging is associated with the network de-differentiation and enhanced inter-network pairing, which is one of the

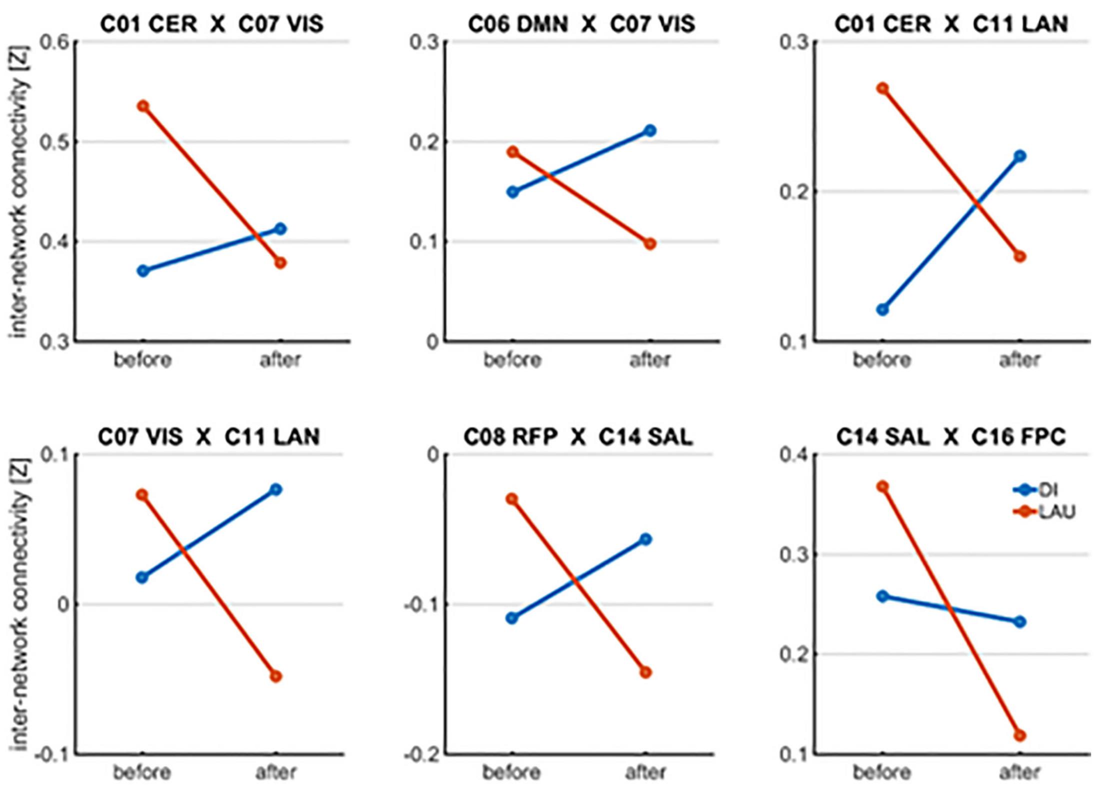

FIGURE 1 | Significant results for group vs. visit interaction in inter-NC.

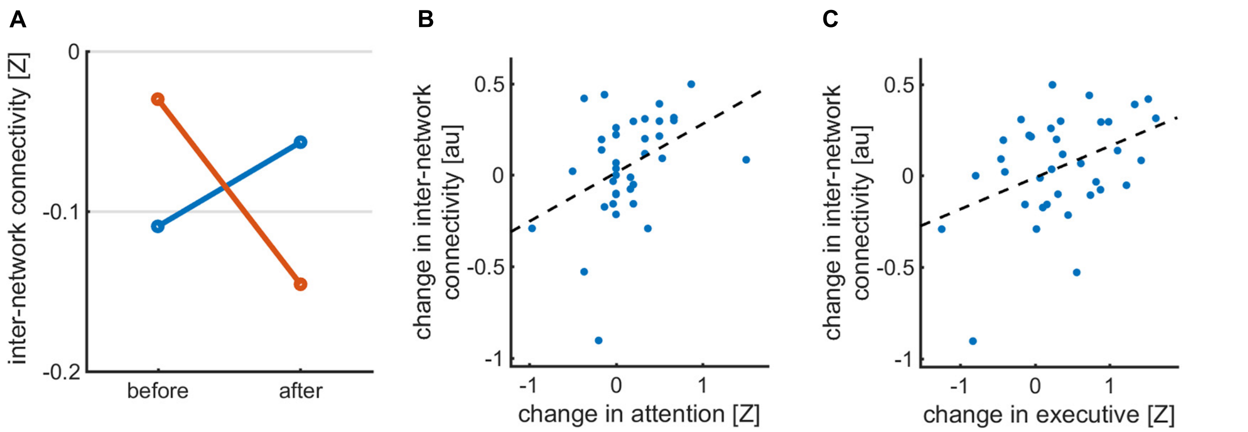

FIGURE 2 | (A) Inter-network connectivity between RFPN and SAL networks in DI and LAU groups before and after the intervention **(B)** correlation between inter-NC between FRP and SAL in DI group and z-scores in attention domain **(C)** correlation between inter-NC between FRP and SAL in DI group and z-scores in executive domain.

well-described neural compensatory mechanisms for decreased modularity and network segregation with age (Geerligs et al., 2015). While several significant results have been found for the group vs. visit interaction, only the inter-network rsFC increases between right frontoparietal network and salience (insulo-opecular) network in the DI group were associated with our cognitive outcome measures, i.e., with z-scores in attention and executive function domains. The salience network comprises anterior cingulate and ventral anterior insular cortices, bilateral Rolandic opercula, with nodes in the amygdala, thalamus, hypothalamus, ventral striatum and specific brainstem nuclei (Menon, 2015; Blefari et al., 2017; Seeley, 2019). The right FP network is located within the right frontal and parietal cortices. Both salience/fronto-opercular and right FP networks (the latter is also referred to as the ventral attention network (Farrant and Uddin, 2015) are engaged in the control of salient (i.e., behaviorally relevant) stimuli processing from internal (interoceptive awareness and bodily self-consciousness) as well as external (outside world) environment (Blefari et al., 2017; Seeley, 2019). They also play important roles in the control of working memory (Wallis et al., 2015). ACC is repeatedly associated with executive functions (Carter et al., 1999), the anterior insula is also functionally connected with frontal regions implicated in executive functions (Eckert et al., 2009). The finding that the DI enhanced this specific inter-network crosstalk related to attention to behaviorally relevant stimuli and to executive functions is novel and future studies should assess the long-term cognitive and behavioral sequelae of these changes.

We also identified increased rsFC between the cerebellum and visual/language networks, and between DMN and visual/language networks. Some of these results have to be taken with caution because of the significant differences in the inter-network connectivity strength between DI and LAU groups already at baseline. On the whole, the abovementioned networks are known to be engaged in movement coordination, and visual and speech processing (Solé et al., 2010; van den Heuvel and Hulshoff Pol, 2010; Manto et al., 2012), thus supporting the notion that DI is an enjoyable multimodal cognitive, movement and social activity that modulates brain plasticity in a specific behaviorally relevant manner.

Study Limitations

One of the study limitations of this study is that there was no active control for the DI group, who would perform, e.g., aerobic activity, such as jogging (Müller et al., 2017). Moreover, due to the low number of MCI subjects in both DI and LAU groups, we could not perform analyses for these groups separately.

In conclusion, dance is a multimodal activity that led to complex intervention-specific brain plasticity changes that were of cognitive relevance.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

IR and ZB contributed to conception, design of the study, and wrote the first draft of the manuscript. ZB, L'N, NN-E, SK, LB, RG, PV, and LS participated in data acquisition. RG, PV, and LS were responsible for DI program preparation and evaluation. RM performed statistical analysis of data. L'N, RM, and IR wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.724064/full#supplementary-material

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
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The Effects of Acute Cardiovascular Exercise on Memory and Its Associations With Exercise-Induced Increases in Neurotrophic Factors

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Due to increasing life expectancy, low-cost interventions to counteract age-related memory impairment have gained popularity. Physical activity has been shown to positively affect memory and hippocampal plasticity in rodents and humans. These effects have been proposed to be mediated by the release of neurotrophic factors. However, studies examining the effects of a single cardiovascular exercise session on human memory have yielded conflicting results. Moreover, it remains unclear whether exercise-induced memory enhancements are related to changes in peripheral neurotrophic factor concentrations. The present study tested whether one bout of cardiovascular exercise during an early phase of memory consolidation, compared to one bout of stretching and toning, positively affected memory. Furthermore, it was analyzed whether exercise-induced changes in the brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) were related to memory enhancement after a single bout of physical exercise. Fifty healthy participants (20–40 years) were randomly assigned to either a cycling group (BIKE) or a stretching and toning group (STRETCH). Participants performed an implicit vocabulary learning task which was immediately followed by physical exercise. Memory for the learned vocabulary was tested 1–2 weeks later. To measure exercise-induced changes in serum neurotrophic factor levels, blood samples were collected at rest (baseline) and immediately after the exercise session. Results did not show a significant difference in memory between the BIKE group and the STRETCH group. However, in the BIKE group, a larger increase in BDNF and VEGF levels was observed than in the STRETCH group. Moreover, the increase in BDNF and memory performance tended to be positively related in the BIKE group. We speculate that the correlation between exercise-increased BDNF levels and memory in the cycling group may indicate an involvement of BDNF in mediating memory processes after acute cardiovascular exercise.

Keywords: learning, memory, physical exercise, neurotrophic factors, BDNF, VEGF

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INTRODUCTION

Life expectancy has been increasing over the past decades (United Nations, 2013). As a result, a growing number of individuals are subject to age-related cognitive decline (Prince et al., 2015). Executive functions, processing speed, and memory are typically mostly affected (Hedden and Gabrieli, 2004). Pathological progression of memory impairments resulting in, for example, Alzheimer's disease, have been reported to be one of the greatest worries of the population about living beyond the age of 75 (Anderson and McConnell, 2007). Thus, there is growing interest in interventions that potentially counteract age-related memory decline.

Regular cardiovascular exercise has been reported to positively influence memory and to induce structural and functional changes in brain regions associated with memory, e.g., the hippocampus. Several weeks or months of regular cardiovascular training were shown to increase performance in a face-name matching task (Griffin et al., 2011), visuospatial short-term memory (Stroth et al., 2009), and immediate and delayed memory for wordlists (Chapman et al., 2013). The increase in cardiovascular fitness after physical exercise training has been found to correlate positively with improvements in episodic memory (Hötting et al., 2012). Moreover, increased hippocampus volume (Erickson et al., 2011; Niemann et al., 2014; Thomas A. G. et al., 2016) and increased hippocampal cerebral blood volume (Pereira et al., 2007) have been reported after a period of regular cardiovascular training. However, evidence in humans concerning the effects of long-term aerobic exercise on memory and associated brain structures in the medial temporal lobe is contradictory. Some studies reported positive effects of an exercise intervention on memory (Stroth et al., 2009; Griffin et al., 2011), while others failed to find a difference in memory between an aerobic exercise group and a control group (Gourgouvelis et al., 2018). In a meta-analysis, Roig et al. (2013) concluded that the positive effects of regular cardiovascular training on long-term memory were not reliably found. Participants' age, training intensity, training duration, and the type of memory tested have been discussed to in part account for the differing results. A better understanding of possible mediators underlying the effects of cardiovascular exercise on memory may resolve some of the observed inconsistencies and shed light on why some training studies yield more consistent exercise-induced memory effects than others.

Similar to chronic cardiovascular exercise, results for single bouts of exercise on memory functions are inconsistent. On the one hand, a single bout of cardiovascular exercise has been shown to positively affect memory (Roig et al., 2013; Bosch et al., 2017b; Dal Maso et al., 2018). On the other hand, other researchers did not find an acute effect of exercise on memory (Hopkins et al., 2012; Basso et al., 2015), or reported enhancements of specific aspects of memory (Coles and Tomporowski, 2008; Suwabe et al., 2017). Inconsistencies in results from human studies are potentially caused by variations in the type of memory tested, exercise intensity, as well as the timing of the exercise session in relation to memory encoding (Roig et al., 2013).

To date, only a few studies have tested the effects of cardiovascular exercise on memory after encoding, i.e., during memory consolidation, and their results have been inconclusive. Beneficial outcomes have been reported for procedural memory when retention was measured 24 h (Roig et al., 2012; Dal Maso et al., 2018) or several days after encoding (Roig et al., 2012; McNerney and Radvansky, 2015). Additionally, an EEG study revealed that better skill retention after exercising was associated with greater beta-band event-related desynchronization in sensorimotor areas, indicating that exercise may improve motor memory by modulating neuronal processing in motor cortices in the early stages of memory consolidation (Dal Maso et al., 2018). However, the effects of cardiovascular exercise after encoding on declarative memory are more equivocal. In one study, participants performed an aerobic exercise session either before or after exposure to a word list which they were instructed to memorize. Memory was tested 60 min and 24 h after learning (Labban and Etnier, 2018). At neither time point did the results indicate a beneficial effect of exercising compared to a no-exercising condition during the consolidation phase. In another study, 6 min of either cycling or relaxing after encoding of emotional images resulted in better memory performance in the cycling group when assessed 60 min after exercise, and thus suggested a beneficial effect of cardiovascular exercise on memory consolidation (Segal et al., 2012). Other researchers compared the effects of 30 min of cycling at low or high intensity to the effects of relaxing after vocabulary learning (Hötting et al., 2016). Cycling after encoding did not enhance the absolute number of recalled words tested 60 min and 24 h after learning. However, participants who exercised at high intensity showed less forgetting between the 60-min and 24-h measurements than participants in the relaxation group. These findings suggested a benefit of cardiovascular exercise directly after encoding on memory consolidation. van Dongen et al. (2016) demonstrated that cycling with a 4-h delay after encoding revealed better performance in a hippocampus-dependent picture-location association task, compared to a group cycling directly after encoding, and a no-exercise control group. In the same study, fMRI data revealed that participants who cycled 4 h after learning showed more distinctive hippocampal representations for the learned associations during retrieval, compared to participants of the other two groups. Furthermore, higher hippocampal pattern similarity correlated with better memory retention across participants. These data suggested that cardiovascular exercise might enhance later stages of memory consolidation more than early phases. In summary, current data on the effects of cardiovascular exercise after encoding on memory performance are ambiguous. Most studies reporting beneficial effects of a single bout of exercise on memory consolidation used sensorimotor tasks. Studies assessing declarative memory are rare and their findings are inconsistent.

Cardiovascular exercise has been proposed to affect memory by increasing levels of neurochemical substances, such as hormones, neurotransmitters, and neurotrophic factors known to be involved in the formation of memories on the neuronal level (Basso and Suzuki, 2017). It has been suggested that early stages of memory consolidation, when the memory trace has most likely not yet reached a stable state, may be particularly susceptible to external influences, such as exercise (Nader and Hardt, 2009). Accordingly, research in both rodents and humans has shown that early memory traces can be altered by stress, physical activity, and pharmacological treatments (McGaugh, 1966; Siette et al., 2014; Vogel et al., 2016).

One of the neurochemical pathways postulated to mediate the effects of cardiovascular exercise on memory involves the exercise-induced alteration of neurotrophic factor levels, such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and insulin-like growth factor 1 (IGF-1; Cotman et al., 2007). In rodents, BDNF, VEGF, and IGF-1 have been shown to be elevated after wheel running (Cetinkaya et al., 2013; Uysal et al., 2015). Moreover, they have been shown to be involved in processes underlying memory formation (Cotman et al., 2007; Voss et al., 2013). BDNF, for instance, is involved in the morphological changes of dendritic spines, long-term potentiation (LTP), and increases neurogenesis by promoting cell survival and proliferation (Bekinschtein et al., 2014; Miranda et al., 2019). LTP is one of the primary mechanisms of synaptic plasticity underlying memory and learning processes. As a key regulator of LTP, BDNF has become a particularly prominent target of research (Miranda et al., 2019). VEGF has been proposed to modulate memory by being involved in angiogenesis and neurogenesis (Fabel et al., 2003; Greenberg and Jin, 2005). IGF-1 is thought to have a neuroprotective function, to play a role in neurogenesis, angiogenesis, synaptic plasticity, and to interact with VEGF to enhance neurogenesis after exercise (Cotman et al., 2007; Fernandez and Torres-Alemán, 2012). Inhibiting BDNF and VEGF action in rodents has been shown to prevent running-induced memory benefits (Vaynman et al., 2004) and neurogenesis (Fabel et al., 2003), respectively. While blocking of IGF-1 activity did not alter the positive effect of exercise on learning, it prevented exercise-induced memory benefits when tested 2 days after learning (Ding et al., 2006). In addition, exercise-induced increases in BDNF, VEGF, and IGF-1 have been shown to correlate with improved spatial learning and memory (Cetinkaya et al., 2013; Uysal et al., 2015). Thus, the results of rodent research suggested that BDNF, VEGF, and IGF-1 mediate the beneficial effects of physical activity on neuroplasticity and memory.

In contrast to rodents, neurotrophic factors cannot be measured directly in the living human brain. Measures are usually taken from blood serum or plasma. In some studies, BDNF, VEGF, and IGF-1 have been shown to cross the blood-brain barrier, indicating a transferability from peripheral to central levels (Pan et al., 1998; Nishijima et al., 2010; Rich et al., 2017; but see Lanz et al., 2012). In humans, a single bout of moderate to intense aerobic exercise has been shown to transiently increase BDNF levels (Ferris et al., 2007; Winter et al., 2007; Hötting et al., 2016; Tsai et al., 2018). In contrast, the evidence for changes in VEGF and IGF-1 levels after cardiovascular exercise in humans is limited in number, and results are equivocal (Griffin et al., 2011; Skriver et al., 2014). Only a few studies reported increases in VEGF and IGF-1 after acute exercise (Kraemer et al., 2004; Kraus et al., 2004; Skriver et al., 2014; Tsai et al., 2018). Associations between the change in neurotrophic factor levels and memory, which might indicate an involvement of neurotrophic factors in memory processes, have not reliably been shown in human studies. Some researchers have demonstrated that increased BDNF levels after exercising correlate with vocabulary learning (Winter et al., 2007) and motor memory (Skriver et al., 2014), while others did not find a relationship with performance in episodic memory tasks (Schmidt-Kassow et al., 2014; Etnier et al., 2016). So far, human studies have failed to find correlations between acute increases in VEGF and IGF-1 after exercising and memory measures (Skriver et al., 2014; Tsai et al., 2018). Hence, a relationship between changes in neurotrophic factors and exercise-induced memory improvements in humans has not been reliably demonstrated to date.

The goal of the present study was to test whether one bout of cardiovascular exercise after encoding had beneficial effects on hippocampus-dependent memory compared to a non-cardiovascular exercise bout after the same memory task. Moreover, we examined whether memory effects were related to exercise-induced changes in neurotrophic factor levels. Young participants were randomized to either a cycling (BIKE) or a stretching and toning training (STRETCH). Immediately after the encoding of an artificial vocabulary, that is during an early stage of memory consolidation, participants engaged in a single bout of physical exercise. Memory was assessed 1–2 weeks after the initial vocabulary acquisition. Blood samples were taken at rest (baseline) and directly after an acute bout of physical exercise to measure serum levels of BDNF and VEGF. We hypothesized that cardiovascular exercise after encoding would result in enhanced memory for the encoded vocabulary compared to stretching and toning. Moreover, it was assumed that cardiovascular exercise, compared to stretching and toning, increased BDNF and VEGF levels. Exercise-induced increases in both neurotrophic factor levels were thought to positively correlate with memory performance.

MATERIALS AND METHODS

Participants

Participants of this study took part in a larger randomized training study that spanned 10 weeks of treatment with repeated learning sessions followed by physical exercise. *A priori* sample size calculation was based on the planned analyses of the larger study project. Here we focus on the acute effects of a single exercise session on learning and memory. Results on the chronic effects of 10 weeks of training will be reported elsewhere.

Eighty-two volunteers were recruited from the city of Hamburg (Germany) using flyers, public advertisements, and the online recruiting platform for psychological experiments at the University of Hamburg. Inclusion criteria comprised age of 18–40 years, an inactive lifestyle (on average ≤ 4 exercise sessions/month during the last 5 years), normal or corrected-to-normal vision, and normal hearing abilities. Exclusion criteria were chronic heart diseases, respiratory diseases, metabolic diseases, musculoskeletal disease, arthropathies, acute infections, chronic or acute neurological or psychiatric diseases, or treatment for neurological or psychiatric diseases in the past 3 years, regular alcohol consumption (>3 times/week), or the regular use of anti-inflammatory medication or medications known to affect the body's immune response. Details of inclusion and exclusion of participants throughout the study are shown in **Figure 1**. The final sample consisted of 50 adults (37 females; age range = 20–40 years; $M = 27.04$, $SD = 5.38$).

Participants received monetary compensation for participation in all training sessions of the larger project. All procedures were carried out in accordance with the Helsinki Declaration guidelines (World Medical Association, 2013). The study was approved by the local ethical board of the Faculty of Psychology and Movement Science at the University of Hamburg. Written informed consent was obtained from all participants.

Design

Data presented in the present article were collected in the first 4 weeks of the longitudinal randomized training study. The larger training study took place over a period of 10 weeks and included multiple training sessions, each consisting of a learning task directly followed by physical exercise (**Figure 2**).

Before the first training session, each participant underwent baseline assessments including a sports-medical examination, a cardiorespiratory fitness test, and baseline blood sampling. Moreover, participants took part in a cognitive assessment, including measurement of verbal intelligence (*Mehrfachwahl-Wortschatz-Intelligenztest*; MWT-B; Helmstaedter et al., 2001) and filled in questionnaires on their physical activity (*Freiburger Fragebogen zur körperlichen Aktivität*; FFKA; Frey et al., 1999) and on depressive symptoms (*Allgemeine Depressionsskala*; ADS; Meyer and Hautzinger, 2001).

After baseline assessments, participants were stratified based on age (over and under 30 years) and then randomly assigned to either a cardiovascular training group (BIKE) or a stretching and toning group (STRETCH). While participants in the BIKE group participated in indoor cycling training, participants in the STRETCH group completed a light stretching and

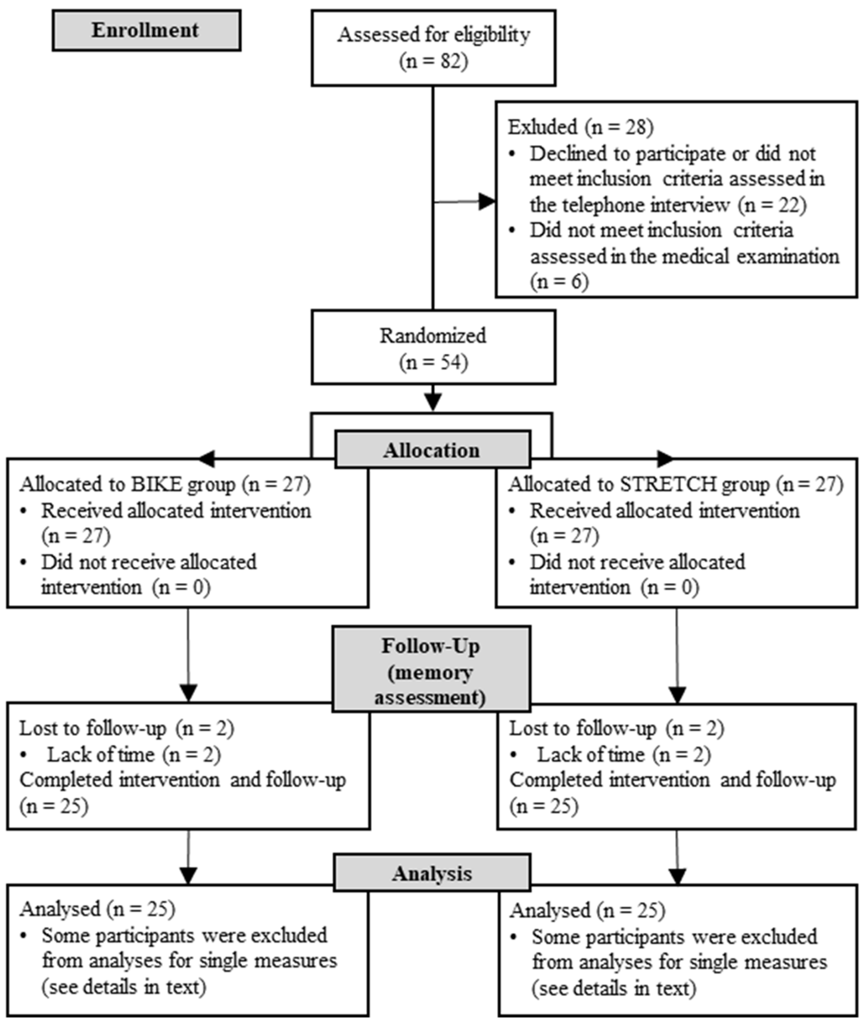

FIGURE 1 | CONSORT flowchart of participants.

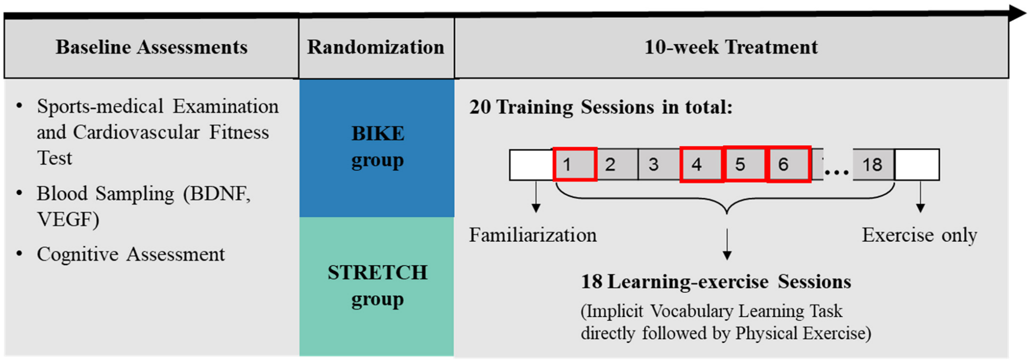

FIGURE 2 | Graphical representation of the study design. This study addressed the effects of a single acute exercise session after learning on memory. Therefore, only retention of the vocabulary learned in the first learning-exercise session (learning-exercise session 1) was analyzed, which was measured 1–2 weeks after the initial acquisition (in learning-exercise sessions 4, 5, and 6).

toning training. Over a period of 10 consecutive weeks, participants in both groups trained on average twice per week, resulting in a total of 20 exercise sessions for each participant. Eighteen of these training sessions were learning-exercise sessions in which participants exercised immediately following an implicit vocabulary learning task. During an initial familiarization session, participants were instructed in the use of the sports equipment and the training protocol. The present study focused only on the acute effects of physical exercise after learning in the first learning-exercise session. Therefore, only recognition of items from learning-exercise session 1, which was measured 1–2 weeks afterwards, were considered (**Figure 2**). The study took place between March 2018 and August 2019.

Sports-Medical Examination and Cardiorespiratory Fitness Test

The sports-medical examination included a medical evaluation of the participants' eligibility for the cardiorespiratory fitness test and participation in the physical exercise training. The examination included documentation of the medical history, a clinical examination, the recording of anthropometric data, urine examination, pulmonary function test, resting electrocardiogram (ECG), and a blood sampling (whole blood count, small blood count, liver enzymes, kidney enzymes, minerals, metabolic parameters, muscle enzymes, total protein, baseline measurement of neurotrophic factors). In addition, participants took part in a standardized stepwise incremental cycle ergometer test (Ergoline ER 900, Monark Ergometric 839E, Cosmed Ergoselect 4) to evaluate their peak oxygen uptake volume (VO_2peak) and individual aerobic-anaerobic threshold. This test began with a warm-up period of 3 min at 50 watts, after which the workload was continuously increased in 50 watt steps every 3 min until subjects indicated complete exhaustion. Lactate measurements and blood pressure measurements were taken before, and every 3 min during the ergometry test as well as 1, 3, and 5 min after its completion. Heart rate and spirometer recordings were continuously measured.

WinLactat software (Mesics GmbH) was used to determine the individual aerobic-anaerobic threshold using lactate measurement, oxygen uptake, and anthropometric data. VO_2peak was taken as a measure of cardiorespiratory fitness. For participants in the BIKE group, the target heart rate for the training was defined as 85% of the heart rate at the individual aerobic-anaerobic threshold, plus/minus five beats.

Implicit Vocabulary Learning Task

For the vocabulary learning task, we adapted the experimental paradigm of Breitenstein and Knecht (2002). Participants repeatedly heard pseudowords while they simultaneously saw black-and-white images on a computer screen. Their task was to decide intuitively whether the presented pseudoword-picture pair was correct or incorrect. The ratio of correct to incorrect pseudoword-picture pairs increased over time. In this way, the more frequently shown pairs were learned to be *correct pairs*. This paradigm has been shown to elicit activity in the hippocampus (Breitenstein et al., 2005). In the study of Breitenstein and Knecht (2002), a total of 50 pseudoword-picture pairs were presented on five consecutive days. As the present study was part of a larger project, the learning task followed the same training principle as described by Breitenstein and Knecht (2002), but used a larger stimulus set to cover more learning-exercise sessions.

Stimuli and Material. Auditory stimuli were taken from a pool of 239 disyllabic German pseudowords, spoken by a female voice, and with a length of 600–1,000 ms (described in detail in Röder et al., 2003). A pilot study was conducted in which 24 participants (19 female; age range = 19–43 years; mean age = 23.8, *SD* = 5.16) rated these pseudowords in terms of their association with real words and pleasantness. Participants heard the pseudowords *via* over-ear headphones. It was their task to type in the perceived pseudoword as well as any associations with real words and to rate the pleasantness of the pseudoword on a scale from 1 to 5 (1 = very pleasant, 5 = very unpleasant). Pseudowords with scores at the extremes of these categories were discarded. Audacity® recording and editing software version

2.1.3[1] was used to either stretch or shorten the remaining pseudowords to a length of 800 ms. After the first author verified that length adjustments did not distort the sound, 150 disyllabic pseudowords, each 800 ms in length with little to no associations with real German words remained. Auditory stimuli were presented with over-ear headphones (AKG k518dj/Sennheiser HD65tv).

The Multilingual Picture (MultiPic) data bank of the Basque Center on Cognition, Brain, and Language was used to obtain the visual stimuli (BCBL; Duñabeitia et al., 2018). The data bank contains 750 drawings of common concrete concepts, which are standardized for visual complexity and name agreement in different languages. One-hundred and fifty black and white images were pre-selected by the first author. Thereafter, two research assistants ensured that the visual stimuli were not related to words that participants had associated with the pseudowords in the pilot study. Visual stimuli were presented with a size of 8 × 8 cm in the center of a computer screen. The distance between participants and the screen was approximately 80 cm.

Procedure. The vocabulary learning task was programmed in Matlab with Psychtoolbox (R2016b, Mathworks Inc.; MATLAB, 2016). At the beginning of each trial, participants were presented with an auditory stimulus (pseudoword). After 200 ms, a visual stimulus (black-and-white picture) was presented until a response was made or the maximum response time of 1,200 ms was exceeded. In case a participant did not respond within the maximum response interval, the message "maximum response time elapsed" appeared on the computer screen and the next trial started. The intertrial interval (ITI) was set to 1,000 ms (**Figure 3**).

Participants' task was to decide intuitively whether the presented pseudoword-picture pair was *correct* or *incorrect*. Responses were given by either pressing the left or the right button on a response device. Participants were instructed to use any two fingers of their dominant hand and to keep them constant across learning sessions. The assignment of *correct* and *incorrect* to the left and right buttons was counterbalanced across participants. Buttons were marked with the labels *correct* and *incorrect*, respectively. Feedback was given at the end of a learning session.

For each participant, a unique set of 150 correct pseudoword-picture pairs was randomly created when initiating the implicit vocabulary learning task for the first time (learning-exercise session 1). Within the learning session, participants were presented with 50 correct pseudoword-picture pairs. These *correct pairs* were mixed with randomly created *incorrect pairs*.

The first learning session comprised two identical blocks, with 100 correct and 100 incorrect pseudoword-picture pairs each. The 100 correct pairs within a block were composed of 50 correct pairs shown twice. By contrast, the 100 incorrect pairs consisted of 50 pseudowords presented twice but paired with different pictures, thus, resulting in 100 unique incorrect pairs. After a 5-min break, the block was repeated. The crucial difference between correct pairs and incorrect pairs was that exactly the same correct pairs were presented twice per block, but each incorrect pair was only encountered once. This presentation pattern led to a ratio of 2:1 for correct:incorrect pairs. The knowledge of correct and incorrect pseudoword-picture pairs was expected to build up from block 1 to block 2 (**Figure 4B**). At the end of the session, participants were given feedback by seeing the percentage of correct answers. This was calculated as the average percentage of correct answers over the two blocks.

Due to the general structure of the learning paradigm across 18 sessions in the larger study project, sessions 1, 2, and 3 each included a different set of 50 correct pseudoword-picture pairs, resulting in a total of 150 correct pseudoword-picture pairs. The 150 correct pairs were unique to each participant and remained the same for each participant across all sessions. These 150 correct pairs presented in sessions 1, 2, and 3 were then mixed with new incorrect pairs and randomly distributed across sessions 4, 5, and 6. The incorrect pairs changed in each session. This means that the 50 correct pairs in sessions 4, 5, and 6 were each composed of, on average, one-third of the correct pairs learned in sessions 1, 2, and 3, respectively (**Figure 4A**). Specifically, of the 50 correct pairs presented in session 1, on average, 16 pairs (min = 11, max = 20) were presented in session 4, 17 pairs (min = 12, max = 23) in session 5, and 17 pairs (min = 10, max = 23) in session 6. Across participants, session 4 took place on average 11.4 days (min = 6, max = 22), session 5 was on average 13.9 days (min = 10, max = 24), and session 6 was on average 16.9 days (min = 11, max = 25) after the first learning session.

D-prime (d') values were calculated as a measure of the participants' ability to distinguish between incorrect pairs and correct pairs. Thereby, correctly identified correct pairs were defined as *hits*; incorrect pairs falsely categorized as correct were defined as *false alarms*. D' was calculated by subtracting the z-scores of the *false alarm rate* (= false alarms/number of incorrect trials) from the z-score of the *hit rate* (= hits/number of correct trials).

In this part of the project, the objective was to determine how many of the correct pairs that had been shown in learning-exercise session 1 were recognized as correct pairs during the second presentation, i.e., in sessions 4, 5, and 6. Therefore, responses to the 50 correct pairs that had been presented in learning-exercise session 1 were extracted from learning-exercise sessions 4, 5, and 6 for each participant (**Figure 4A**). The hit rate for the extracted 50 correct pairs was used to calculate recognition performance. False alarms were calculated by averaging the false alarm rate of sessions 4, 5, and 6; separately for blocks 1 and 2. Two measures of recognition performance were analyzed: the memory score extracted from the first blocks of sessions 4, 5, and 6 (d' of block 1) and within-session learning (d' from block 1 to block 2) for the extracted words from sessions 4, 5, and 6.

Blood Sampling and Analysis of Neurotrophic Factors

At baseline and in one learning-exercise session, 7.5 ml blood was collected from the elbow vein. The baseline sample

[1]Audacity® software is copyright © 1999-2020 Audacity Team. The name Audacity® is a registered trademark of Dominic Mazzoni.

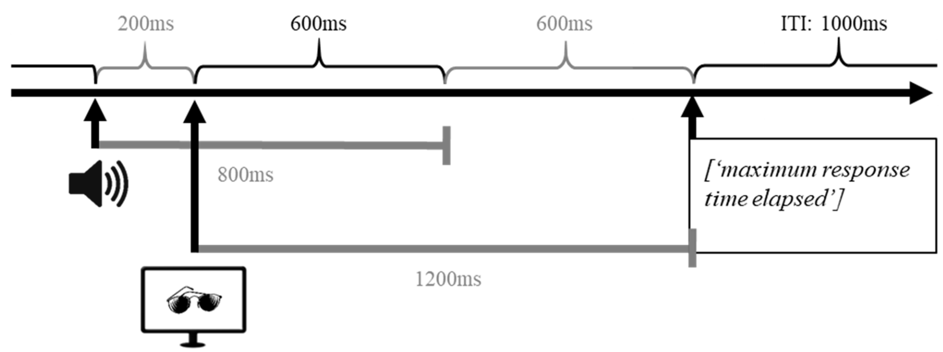

FIGURE 3 | Graphical representation of the time course of a single trial in the implicit vocabulary learning task. In each trial, participants were first presented with an auditory stimulus (pseudoword); 200 ms after the onset of the auditory stimulus a visual stimulus (black-and-white picture) was presented until either participant made a response or the maximal response time was reached. If participants did not respond within the response interval of 1,200 ms, the message "maximum response time elapsed" was displayed on the screen. After 1,000 ms the next trial was initiated.

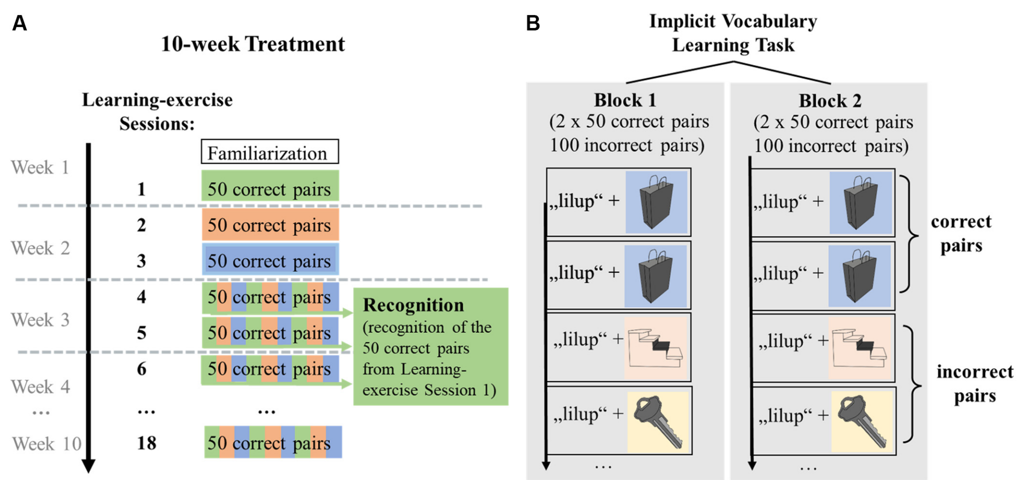

FIGURE 4 | Graphical representation of the distribution of correct pseudoword-picture pairs over learning-exercise sessions, extraction of recognition performance and within-session learning. **(A)** Distribution of correct pseudoword-picture pairs across learning-exercise sessions. In learning-exercise sessions 1, participants encountered 50 correct pseudoword-picture pairs, which were randomly distributed across sessions 4, 5, and 6 (indicated by green color). To measure recognition of the vocabulary encoded in learning-exercise session 1, participants' responses to the 50 correct pairs shown in session 1 were extracted from sessions 4, 5, and 6 (shown in green). Data of learning-exercise sessions 7–18 were not analyzed for the acute effects of exercise. **(B)** Within-session learning. A learning session was divided into two blocks. Within a block, each of the 50 correct pairs was shown twice (indicated by blue color), resulting in 100 correct pairs. By contrast, the 100 incorrect pairs consisted of 50 pseudowords presented twice but paired with different pictures, thus, resulting in 100 unique incorrect pairs per block. Each of the incorrect pairs was shown only once (indicated by yellow and orange color). This ratio of correct to incorrect pairs allowed learning within a session from block 1 to block 2. Stimuli were repeated in the second block, in the same order.

was taken during the sports-medical examination before the cardiovascular fitness test, and two further samples were collected in one of the first learning-exercise sessions (session 1, 2, 3, or 4), one sample directly before exercise and the second sample directly after exercise. Thus, each participant had two resting measurements, one at baseline and one directly before exercising, as well as one post-exercise measurement. In which of the learning-exercise sessions 1–4 the blood samples were taken was dependent on the availability of a qualified staff member. The number of participants assessed in learning-exercise sessions 1, 2, 3, and 4, respectively, did not differ between the BIKE and STRETCH group (**Table 1**).

Baseline blood samples were centrifuged within 10 min after collection. For technical and organizational reasons, blood samples collected before exercise had to be stored at room temperature until the sampling after exercise had been performed. Therefore, the blood samples taken before exercise had a longer average time interval between collection and centrifugation, compared to the blood samples taken after exercise. Neurotrophic factor levels measured in blood serum could be influenced by clotting time with longer time intervals

TABLE 1 | Frequency distribution of the learning-exercise sessions in which blood sampling was performed.

	Learning-exercise session 1	Learning-exercise session 2	Learning-exercise session 3	Learning-exercise session 4
BIKE	2	10	13	1
STRETCH	4	9	11	0

TABLE 2 | Timing of blood sampling at baseline and after exercise as Mean and Standard Deviation in brackets.

	BIKE	STRETCH
Days between baseline and after exercise blood sampling (in days)	18.9 (6.88)	18.6 (8.91)
Time of baseline sampling (in hours)	12:58 (2:55)	12:53 (3:09)
Time of sampling after exercise (in hours)	14:45 (4:41)	14:10 (4:54)
Absolute time difference (after exercise – baseline; in hours)	4:43 (3:12)	3:50 (3:12)
Relative time difference (after exercise – baseline; in hours)[a]	−1:58 (5:25) min = 7:30, max = −11:30	−1:10 (4:55) min = 7, max = −11

[a]*Negative values: blood sampling at baseline was conducted earlier in the day than blood sampling after exercise.*

between blood collection and centrifugation increasing serum levels of BDNF and VEGF (Webb et al., 1998; Gejl et al., 2019). Comparing serum levels of BDNF and VEGF at baseline (during the medical examination) and immediately before exercising in the learning-exercise session 1, 2, 3, and 4, respectively, revealed a significantly larger mean level across participants for samples collected before exercising compared to baseline, although both were taken at rest. *Post hoc*, we ran a control experiment in four additional participants and varied the time intervals from blood sampling to centrifugation (0, 1.0 h, 1.5 h, 2.0 h, 3.0 h), which showed an increase in BDNF and VEGF levels during the 1st hour of clotting and a plateau for longer clotting times. Therefore, to assess the effect of acute exercise on neurotrophic factor levels, blood samples after exercise in sessions 1, 2, 3, and 4, respectively, were compared with the blood samples taken at baseline. Samples taken immediately before exercising in sessions 1, 2, 3, and 4, respectively, were not considered for analyses. On average, blood samples after exercise were taken 2 h later in the day than the baseline samples. However, this was the case in both groups, making it unlikely that circadian influences could account for group differences in exercise-induced changes in neurotrophic factors (**Table 2**). The blood collection procedure was the same for both groups. Thus, any group difference cannot be accounted for by how the blood samples were taken.

All blood samples were centrifuged at room temperature for 10 min at 4,000 RPM. Three milliliters of isolated serum were filled in cryotubes and directly stored at −24°C until transported to the Bernhard Nocht Institute for Tropical Medicine in Hamburg (BNI) for storage at −80°C on nitrogen for later analysis of the serum concentration of BDNF and VEGF. BDNF concentrations were assessed with an ELISA kit (Human BDNF ELISA MAX Deluxe Set provided by BioLegend (Cat.No 446604, Lot 8276603). Quantification was performed with an ELISA Reader (Photometer). For analysis of VEGF, BioLegend's LEGENDplex multiplex assay (Custom Human 9-plex Panel, BioLegend, USA) was used. 3 μl of each serum sample was diluted four-fold (1:4 dilution). Samples were placed on 96-well V-bottom Polypropylen plates provided by GreinerBio. For quantification, the ACCURI C6 FlowCytometer (Becton Dickenson) was used with a detection limit of 2.4 pg/ml.

The concentration of neurotrophic factors in pg/ml was used as a dependent variable. Due to errors in the laboratory analyses, data from one participant were missing for the baseline measurement (BIKE) and data from two participants were missing for both the baseline measurement and the measurement after exercise (one BIKE, one STRETCH).

Physical Exercise

Cardiovascular Exercise Training (BIKE)

Training sessions in the BIKE group included cardiovascular training on a cycle ergometer (Taurus Indoor Bike IC50) using video based indoor cycling instructions (CyberFitness GmbH[2]). Across training sessions, different videos were shown in a fixed order. These videos alternated between showing the instructor on an indoor bike and a first-person perspective of a cyclist riding through various landscapes. The videos included a short, low-impact warm-up, after which participants exercised for approximately 45–55 min at their target heart rate as determined by the cardiorespiratory fitness test. Participants were equipped with a fitness and activity tracker (Polar A300, Polar Electro Oy, Finland) which continuously recorded their heart rate. They were instructed to regularly check their heart rates on the activity tracker. The training ended with a cool-down and brief stretching.

Stretching and Toning (STRETCH)

In the STRETCH group, training sessions were instructed *via* videos which were selected from an online fitness platform (fitnessRAUM.de GmbH[3]). Training sessions included a wide range of low-impact exercises. Among them were exercises

[2]https://www.cyberconcept.de/cybercycling/
[3]https://www.fitnessraum.de/

to prevent back pain, instructions on how to sit and stand properly, light gymnastics such as sit-ups or low-impact push-ups, stretching, and relaxation exercises. Some videos invited participants to use equipment, such as a resistance band or a water bottle as a dumbbell. To match the training duration of the BIKE group, each training session in the STRETCH group contained several videos, which participants watched in a fixed order. Heart rate was continuously monitored, but participants were not asked to pay attention to their heart rate during the training.

Statistical Analysis

Data were analyzed using the statistical software R (version 3.5.1, R Core Team, 2018). Independent samples t-tests were used to compare the BIKE and the STRETCH group at pre-assessment. The *lme4* package (Bates et al., 2015) was used to analyze performance in the vocabulary learning task and neurotrophic factor levels with linear mixed effect models (LMMs). Group was inserted as a factor in all models, with the STRETCH group serving as reference level. The fixed and random effects of each model are described in detail below. If not stated otherwise, all models included the covariates gender and age, which was centered at the mean. The package *parameters* (Lüdecke et al., 2020) were used for obtaining *p*-values and confidence intervals, using Wald-test approximation. *Post hoc* tests were performed with pairwise comparisons of estimated marginal means and the package *emmeans* (Lenth, 2019). Corrections for multiple comparisons were conducted following the Tukey method. The significance level was set to $p < 0.05$ for all analyses.

Implicit Vocabulary Learning Task

Memory scores in the first block of the recognition sessions (d' of block 1) were compared between the groups using an independent sample t-test. For analysis of within-session learning, an LMM was set up with d' values of the recognition sessions as dependent variables. As fixed effects, the model included the interactions and main effects of group and block (block 1, block 2). *Block 1* served as the reference of the factor block. Random effects included individual intercepts for each participant as well as individual slopes for the effect of the block. This allowed participants an individual learning slope from block 1 to block 2. To account for different time intervals between learning-exercise session 1 and learning-exercise sessions 4–6, the mean time interval in days was inserted as a covariate. The main parameter of interest in this model was the interaction of group and block, to test whether groups differed in within-session learning.

Neurotrophic Factors

A separate model was set up for each neurotrophic factor. Neurotrophic factor levels were included as the dependent variables. As fixed effects, models contained the interaction and main effects of time (baseline, after exercise) and group. *Baseline* served as the reference for the factor time. Random effects included individual intercepts for each participant. The main parameter of interest in this model was the interaction between group and time. This term described whether there were differences in the change of neurotrophic factors from baseline measurement to after exercise measurement between the two groups. Exclusion criteria for single data points were values more than three standard deviations above the mean. VEGF data of one participant of the STRETCH group were removed as outliers.

Regression Analysis

Regression models were used to explore possible associations between changes in neurotrophic factor levels from baseline to after exercise and memory performance 1–2 weeks after learning (described in "Implicit Vocabulary Learning Task" section). Memory performance in the recognition sessions was indicated by two measures: memory score in the first blocks (d' of block 1) and within-session learning, calculated as the difference in d' from blocks 1 to blocks 2 (block 2 − block 1). Changes in BDNF and VEGF levels were calculated by subtracting the levels measured at baseline from those after exercise (after exercise − baseline). Change scores of neurotrophic factors were z-standardized before they were entered in the respective model. In total, four separate models were set up. In these models, the memory score in block 1 and within-session learning was predicted from the interaction of change in neurotrophic factor level and group. All models included the following covariates: age (centered at the mean), gender, the average number of days between session 1 and recognition, and the time difference (time of the day) between baseline and after exercise blood sampling. Pearson's partial correlations (adjusted for covariates) were conducted to explore possible associations of memory with changes in neurotrophic factors in the single groups. For the change scores of BDNF and VEGF, participants were excluded if the change was more than three standard deviations above the mean. This was the case for VEGF of one participant in the BIKE group.

RESULTS

The BIKE and STRETCH groups did not differ in age, cardiorespiratory fitness (VO_2peak), body mass index (BMI), and depression score at baseline (**Table 3**).

In the first learning-exercise session, the BIKE group trained with a significantly higher heart rate (M = 143 beats/min, SD = 13.83) compared to the STRETCH group (M = 92 beats/min, SD = 8.55); $t_{(40.26)} = 15.42$, 95% CI: [43.8, 57.0], $p < 0.001$.

Comparing d' in block 1 and within-session learning in the first learning-exercise session revealed no significant difference between the BIKE and the STRETCH group (**Table 3**; no significant group × block interaction ($ß = -0.02$, 95% CI [−0.21, 0.17], $p = 0.838$).

Implicit Vocabulary Learning Task

The comparison of d' in block 1 of the recognition sessions revealed no significant difference between the groups; $t_{(46.80)} = -0.30$, 95% CI [−0.25, 0.19], $p = 0.762$.

Analysis of d' values from block 1 to block 2 revealed a significant main effect of block ($ß = 0.24$, 95% CI [0.14, 0.34], $p < 0.001$) but no significant group × block interaction ($ß = 0.02$, 95% CI [−0.12, 0.16], $p = 0.774$). Hence, participants of both groups increased their performance from block 1 to block 2,

TABLE 3 | Group characteristics at baseline as Mean with Standard Deviation in brackets.

	BIKE	STRETCH	p-value[a] [95% CI]
n	25	25	
Male/Female	6/19	6/19	
Age	27.4 (5.82)	26.7 (5.03)	0.679, [–3.73, 2.45]
Verbal intelligence[b]	99.2 (10.10)	107.1 (12.55)	**0.030**, [0.82, 14.92]
VO_2peak	33.7 (5.89)	34.3 (6.14)	0.732, [–2.84, 4.01]
BMI	24.2 (4.03)	23.5 (3.73)	0.523, [–2.92, 1.50]
Depression Score	12.9 (6.83)	12.4 (5.27)	0.747, [–4.03, 2.92]
D' of Block 1 in the first learning-exercise session	0.11 (0.31)	0.19 (0.21)	0.225, [–0.24, 0.06]
Within-session learning in the first learning-exercise session (Block 2 – Block 1)	0.15 (0.31)	0.17 (0.34)	0.834, [–0.20, 0.17]

Note. Bold print indicates significance at p < 0.05. [a]Independent t-test; [b]Measured with the MWT-B. MWT-B data of seven participants who were non-native German speakers (4 BIKE group, 3 STRETCH group) were excluded from the analysis.

but there was no difference in within-session learning between the groups. In sum, when encountering the correct pseudoword-picture pairs learned in session 1 a second time, there was no difference in memory performance between the BIKE and the STRETCH group (**Figure 5**).

Neurotrophic Factors

Analysis of BDNF levels from baseline to after exercise showed a significant main effect of time ($ß$ = 591, 95% CI, [154, 1,028], standardized $ß$ = 0.32, p = 0.008), and a significant interaction of time × group ($ß$ = 715, 95% CI [95, 1,336], standardized $ß$ = 0.34, p = 0.037). *Post hoc* tests indicated that both groups had significantly higher BDNF levels after exercise compared to baseline. However, this increase was significantly larger in the BIKE (after exercise—baseline: $ß$ = 1,307, 95% CI [853, 1,760], $p < 0.001$) compared to the STRETCH group ($ß$ = 591, 95% CI [143, 1,039], p = 0.011).

Results for VEGF from baseline to after exercise yielded a significant interaction of time × group ($ß$ = 31.6, 95% CI, [1.68, 61.49], standardized $ß$ = 0.19, p = 0.038). *Post hoc* tests indicated the BIKE group's VEGF levels significantly increased after exercise (after exercise—baseline: $ß$ = 49.5, 95% CI [28.0, 71.0], $p < 0.001$) while showing no significant change for the STRETCH group (after exercise—baseline: $ß$ = 17.8, 95% CI [−4.0, 39.5], p = 0.107). Both the changes in BDNF and VEGF level are depicted in **Figure 6**.

To test whether the time of day might have influenced the effects, we ran additional models including the time of blood sampling as covariate (as numeric from 0:00 h). Including the time of blood sampling into the model did not change the pattern of results and the group × time interaction of both models remained significant (BDNF time × group: p = 0.027, VEGF time × group: p = 0.037).

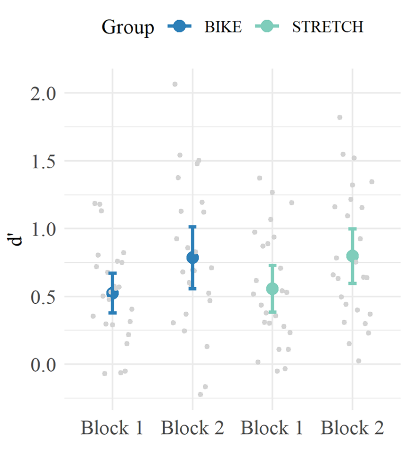

FIGURE 5 | Mean d' values for Block 1 and Block 2 of the recognition sessions. For each participant, the data of the correct pairs encountered in learning-exercise session 1 were extracted from learning-exercise sessions 4–6 and used to calculate d' values. Means are depicted in blue for the BIKE group and in green for the STRETCH group. Error bars depict 95% confidence intervals. Data of single participants are depicted in gray.

Associations of Changes in Neurotrophic Factor Levels With Memory

We tested whether the exercise-induced increase in neurotrophic factors correlated with the memory score in block 1 and with within-session learning in the recognition sessions.

For the memory score in block 1, models revealed a marginal significant interaction between the change in BDNF and group ($ß$ = 0.26, standardized $ß$ = 0.44, 95% CI [−0.001, 0.512], p = 0.051). Partial correlations, separately for each group, indicated a marginal significant correlation between BDNF increase and memory score in the first block for the BIKE group ($r_{(23)}$ = 0.41, p = 0.082), but not in the STRETCH group ($r_{(24)}$ = −0.21, p = 0.364). For within-session learning, models indicated a significant interaction between the change in BDNF and group ($ß$ = 0.18, standardized $ß$ = 0.46, 95% CI [0.02, 0.33]; p = 0.035). Partial correlations revealed a marginally significant positive association between the change in BDNF and within-session learning in the BIKE group ($r_{(23)}$ = 0.40, p = 0.086), but not in the STRETCH group ($r_{(23)}$ = −0.27, p = 0.253). Partial correlations are depicted in **Figure 7**. We tested whether these correlations may be confounded by possible relationships between baseline BDNF and memory. Results showed no significant correlation between baseline BDNF levels and the memory score extracted from the first blocks of sessions 4, 5, and 6 (d' of block 1; $r_{(47)}$ = −0.06, p = 0.725) and within-session learning (d' from block 1 to block 2) for the extracted words from sessions 4, 5, and 6 ($r_{(47)}$ = −0.12, p = 0.429).

For both memory measures, there were no significant interactions between group and change in VEGF levels from baseline to after exercise (all $p > 0.221$). Collapsing data of both

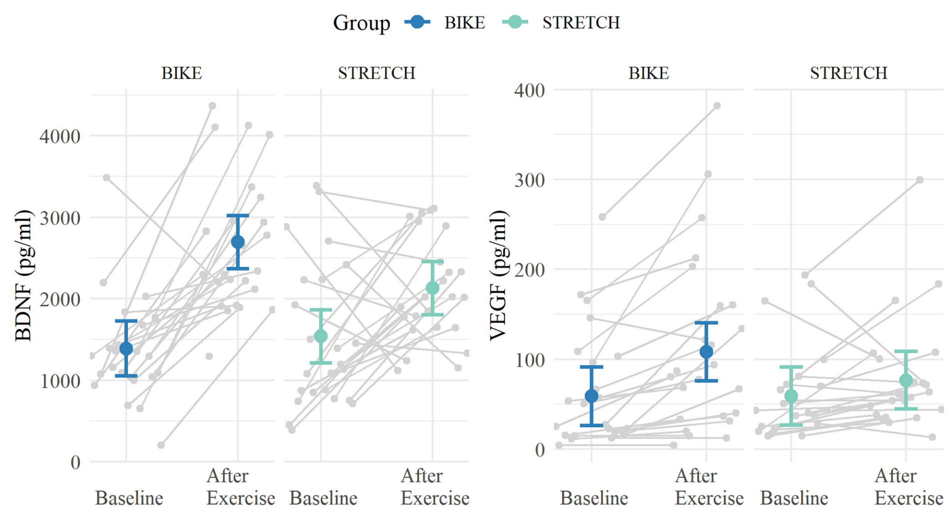

FIGURE 6 | Means of BDNF and VEGF levels at baseline and directly after one bout of exercise. Blood was collected at rest in the sports medical examination (baseline) and directly after one bout of exercise in one of the first learning-exercise sessions 1–4. Means are depicted in blue for the BIKE group and in green for the STRETCH group. Error bars depict 95% confidence intervals. Data of single participants are depicted in gray.

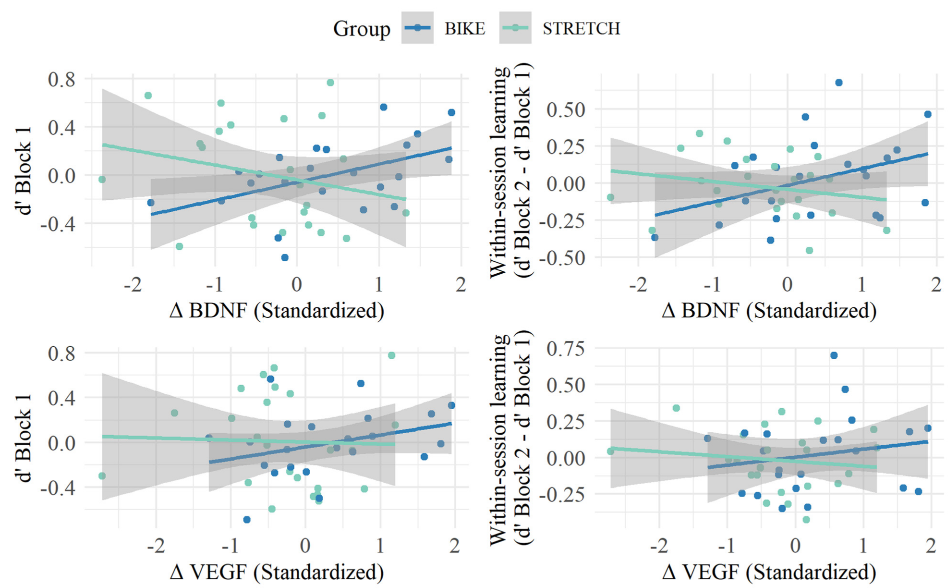

FIGURE 7 | Associations between memory score in Block 1 (left) and within-session learning (right) in the recognition sessions and the change in BDNF (top) and VEGF (lower) levels from baseline to after exercise. Partial residual plots of the relationship between memory in the recognition sessions and the standardized change in neurotrophic factor levels (BDNF, VEGF) from baseline to after a single bout of exercise (after exercise – baseline); r adjusted for age, gender, the average number of days between learning-exercise session 1 and recognition, and the time difference between baseline and after exercise blood sampling. Regression lines are blue for the BIKE group and green for the STRETCH group. Circles in the respective colors represent single participants. Gray shades indicate 95% confidence bands.

groups did not show an association between VEGF change and memory measures (all $p > 0.550$).

DISCUSSION

The aim of this study was to test whether a single bout of cardiovascular exercise carried out in the early stages of memory consolidation improves memory as assessed with an artificial vocabulary learning task. In addition, the effects of physical exercise on serum levels of BDNF and VEGF were determined in order to explore whether they mediate exercise-induced memory changes. Results did not indicate a beneficial effect of cycling on memory measured 1–2 weeks after initial acquisition compared to stretching and toning. Analyses of serum neurotrophic factor levels revealed significantly larger BDNF and VEGF increases after physical exercise in the cycling group compared to the stretching and toning group. Exercise-induced changes in BDNF levels tended to positively correlate with memory measures in the BIKE group, but not in the STRETCH group.

It has been hypothesized that physical exercise might enhance memory, possibly through the acute exercise-induced release of neuromodulatory factors, such as dopamine, norepinephrine, cortisol, and BDNF, which are known to be involved in memory consolidation (McGaugh, 2000; Siette et al., 2014; van Dongen et al., 2016; Miranda et al., 2019). In the present study, participants exercised immediately after encoding a new vocabulary. Thus, encoding conditions were held constant across groups, but the activity of the groups differed in the early stages of memory consolidation. Yet, the results of the present study did not provide evidence that cycling directly after the encoding phase was beneficial for memory consolidation, compared to stretching and toning. The timing of exercise relative to memory encoding has been discussed as a crucial factor modulating the benefits of acute exercise on memory processes (Roig et al., 2016). A meta-analysis reported larger effect sizes for memory improvements when exercise was implemented before than after learning (Roig et al., 2013). The larger effect sizes might be due to the combined effect of exercise on encoding and consolidation processes because the physiological adaptations induced by a bout of cardiovascular exercise performed before encoding are likely to persist into the early stages of memory consolidation. Roig et al. (2016) suggested that a close temporal coupling of exercise with memory processes is the key factor for memory improvements to occur. This is supported by studies that systematically varied the timing of exercise relative to a memory task. Results showed beneficial effects of an acute bout of cardiovascular exercise on visuo-motor memory regardless of whether exercise was performed immediately before or after motor learning, but not when exercise and learning were separated by 1 h longer time intervals (Statton et al., 2015; Thomas et al., 2016a). van Dongen et al. (2016) did not report beneficial effects of cardiovascular exercise on memory for picture-location associations and hippocampal pattern separation when exercise was performed immediately after learning. However, exercise improved memory when performed 4 h after learning, thus, in the late stages of memory consolidation (van Dongen et al., 2016). The authors discussed that levels of neurotrophins supporting synaptic plasticity might be naturally lower several hours after learning and thus, exercise upregulating the release of these factors might have a larger impact on memory outcomes during late consolidation stages. However, these explanations are still speculative and a possible more pronounced effect of delayed exercise relative to encoding on memory consolidation needs replication in further studies.

Moreover, studies differed with regard to the memory tasks used and thus, the addressed underlying neuronal networks. In the present study, we assessed the retention of items encoded in an implicit paired association task. fMRI data suggested that successful learning in this task is associated with hippocampal activity and increased functional coupling between the left hippocampus and cortical association areas as the left fusiform gyrus and the left inferior parietal lobe (Breitenstein et al., 2005). Results of previous acute exercise studies assessing memory in associative learning tasks have yielded inconsistent results with some studies showing better memory for associations encoded prior to exercise (van Dongen et al., 2016; Bosch et al., 2017a), while others did not find better memory for associations learned before exercise (McNerney and Radvansky, 2015; Hötting et al., 2016). Findings seemed to be more consistent for motor learning tasks. For instance, several studies reported positive effects of a single cardiovascular exercise session after practicing visuo-motor tracking tasks (Roig et al., 2012; Thomas et al., 2016b; Dal Maso et al., 2018). Learning in visuo-motor tasks has been shown to activate the basal ganglia, cerebellum, and motor cortices (Doyon et al., 2009) and have been found to be spared after hippocampal lesions (Corkin, 1968). Therefore, one could speculate that in humans, the brain structures responsible for motor learning are in particular sensitive to the beneficial effects of acute cardiovascular exercise. Yet, this is contradictory to results in rodents reporting very reliable exercise-induced functional and structural changes in the hippocampus after exercise (reviewed in Cotman et al., 2007; van Praag, 2008). Moreover, fMRT results in humans showed task-dependent modulations of hippocampal activity after acute exercise (Bosch et al., 2020). Future studies contrasting hippocampus-dependent learning tasks and hippocampus-independent learning tasks in humans might shed light on the question of whether there is a task-dependent effect of physical exercise in phases of early memory consolidation (McNerney and Radvansky, 2015).

In addition, studies analyzing the effects of acute cardiovascular exercise on memory differed in the intensity of the physical exercise and the fitness status of participants (Roig et al., 2013). In the present study, the BIKE group received cardiovascular training of moderate intensity. The training heart rates of participants in the BIKE group were adjusted to the individual aerobic-anaerobic threshold. Thus, the relative training intensity was similar for all participants and we made sure that participants trained within the aerobic range. Moreover, the heart rate was measured in the STRETCH group as well, confirming a significant mean difference of 44 beats/min between groups. Some recent studies have suggested that higher physical exercise intensities more reliably improve memory performance in acute exercise designs compared to low or moderate intensity exercise (Winter et al., 2007; Etnier et al., 2016; Thomas et al., 2016b). However, the effect of training intensity is additionally dependent on individuals' baseline fitness and age.

It has been shown that more fit and regularly active participants showed stronger increases in cognitive functions after acute cardiovascular exercise compared to less fit and untrained peers (Chang et al., 2012; Hopkins et al., 2012). Participants in the present study were sedentary and had relatively low cardiovascular fitness levels (average peak oxygen uptake volume, VO_2peak, of 34 ml/kg/min) compared to normative samples in that age range (Laukkanen and Held, 1999). Most other studies reporting positive effects of acute cardiovascular exercise on memory included participants with higher fitness levels of above a VO_2peak of 40 ml/kg/min (Winter et al., 2007; Etnier et al., 2016; Thomas et al., 2016b; Bosch et al., 2017b). It remains a task of future research to further elucidate the extent to which variables such as prior physical activity, intensity of the physical exercise, or the interaction of both factors influence the effect of acute cardiovascular exercise on memory.

Due to the general study design of the larger project, memory for the pseudoword-picture pairs of the implicit vocabulary learning task was assessed 1–2 weeks after initial encoding and was spread over three separate sessions that took place on different days. Moreover, participants were exposed to further pseudoword-picture pairs between initial encoding and memory assessment, possibly causing interference effects. It is, therefore, possible that the study design may have masked potential effects on the behavioral level.

Exercise-induced changes in neurotrophic factor levels have been suggested to at least partly mediate the positive effects of cardiovascular exercise on memory (Cotman et al., 2007; El-Sayes et al., 2019). Consistent with the literature, BDNF levels increased significantly more after acute cardiovascular exercise compared with non-cardiovascular exercise (Winter et al., 2007; Hötting et al., 2016; Tsai et al., 2018). So far, only a few studies have investigated the response of VEGF levels to acute cardiovascular exercise and reported mixed findings (Landers-Ramos et al., 2014; Skriver et al., 2014; Tsai et al., 2018; Kujach et al., 2020). The present results indicated an increase of VEGF levels after cycling, but not after stretching and toning. Thus, a bout of moderate intensity cardiovascular exercise seems to increase both BDNF and VEGF levels in young, untrained adults.

Regarding the relationship between exercise-induced changes in BDNF levels and memory, results yielded significant differences between the BIKE and STRETCH groups. Follow-up analyses of the present study showed marginally significant associations between a larger increase in BNDF and better performance in measures of memory (memory performance in block 1 and within-session learning in the recognition sessions) only in the BIKE group. Correlation coefficients were of moderate strength. The sample size calculation for the present study was based on the main hypothesis of the larger project predicting a group difference in memory improvements across multiple learning sessions. Thus, the relatively small sample size in the BIKE group was not sufficient to test for significant correlations in such a range and needs replication in larger samples. Nonetheless, results of the present study add to the literature showing a positive relationship between the increase in BDNF and memory performance, suggesting that BDNF may be related to memory improvement after exercise (Schmidt-Kassow et al., 2014; Skriver et al., 2014; but see Etnier et al., 2016; Bosch et al., 2017a,b).

Although BDNF correlated with memory in the BIKE group, there was no difference in memory parameters between the BIKE and the STRETCH group. It has been assumed that higher levels of neuromodulatory substances (BDNF, VEGF) after encoding might facilitate memory consolidation (Miranda et al., 2019; van Dongen et al., 2016). BDNF levels in response to cardiovascular exercise have been shown to increase in an intensity-dependent manner, with higher intensities inducing larger increases (Ferris et al., 2007; Winter et al., 2007; Etnier et al., 2016; Hötting et al., 2016). Moreover, exercising with higher intensity than in the present study is known to increase levels of further neuromodulators, such as noradrenalin, adrenalin, and lactate (Winter et al., 2007; Skriver et al., 2014; Basso and Suzuki, 2017). It could, thus, be speculated that the cycling intensity in the present study did not sufficiently enhance BDNF levels and did not induce the secretion of neurochemical substances which would have been required for behavioral benefits after acute cardiovascular exercise (but see Bosch et al., 2017b for contrasting evidence).

In line with earlier research, the increase in VEGF did not correlate with memory and no group differences were found for the relationship between acute exercise-induced changes in VEGF levels and memory (Skriver et al., 2014). However, literature relating to exercise-induced VEGF changes and memory in both chronic and acute study designs is limited, and results are equivocal (Skriver et al., 2014; Woost et al., 2018). In observational studies, higher VEGF levels have been positively associated with larger hippocampal volume, less hippocampal atrophy, and less cognitive decline over time (Hohman et al., 2015) as well as with a decreased risk for Alzheimer's disease (Mateo et al., 2007), indicating that VEGF might be beneficial for memory-related processes.

Results from rodent studies have supported the involvement of BNDF and VEGF in exercise-induced memory improvements and their associated structural changes in the brain, such as synaptogenesis, neurogenesis, and angiogenesis (Fabel et al., 2003; Vaynman et al., 2004; Cotman et al., 2007; Uysal et al., 2015; El-Sayes et al., 2019). While VEGF has mainly been related to neurogenesis and the growth and protection of the vasculature (Greenberg and Jin, 2005; El-Sayes et al., 2019), BDNF, in particular, has received a lot of attention due to its role in long-term potentiation, that is synaptic plasticity essential for memory consolidation (Miranda et al., 2019). Methodological differences between rodent and human research may partially explain inconsistent results found with respect to associations between neurotrophic factor levels and memory in humans (Schmidt-Kassow et al., 2014; Skriver et al., 2014). In contrast to rodents, invasive procedures to manipulate or measure levels of neurotrophic factors in the brain cannot be applied in humans. Therefore, they are typically measured peripherally in serum or plasma. It is unclear how these peripherally measured neurotrophic factors are related to the levels in the brain (Pan et al., 1998; Lanz et al., 2012; Rich et al., 2017). Moreover, local increases, for example in the hippocampus, cannot be determined by peripheral measures. Therefore, systemic measurements in humans might not reliably capture changes in neurotrophic factors and their relationship to memory, as they may increase and act particularly at the local level in the brain.

Among the limitations of the present study is the blood sampling procedure. Serum BDNF levels were increased after lightly exercising in the STRETCH group (average heart rate of 94 beats/min). Previous studies did not report BDNF increases after exercising at comparable intensity (Schmidt-Kassow et al., 2014; Hötting et al., 2016). For organizational and technical reasons, blood samples collected after exercise were stored at room temperature until they were transported to the centrifuge. This storage possibly caused the release of BDNF from platelets and may be responsible for the unexpected increase of BDNF levels in the STRETCH group (Webb et al., 1998; Gejl et al., 2019). Thus, the absolute values of neurotrophic factors in the present study should be interpreted with caution, in particular when comparing absolute serum values to those reported in previous studies. Nevertheless, given that the sampling procedure and storage time were the same for both groups, it is possible to unequivocally interpret group differences in BDNF change. Additionally, taking blood samples on different days and at different times might have introduced additional variance in the levels of neurotrophic factors due to time- and day-dependent fluctuations (Hetland et al., 2008; Piccinni et al., 2008). However, the time difference and number of days between baseline and post-exercise blood sampling were similar between the BIKE and STRETCH groups, rendering it highly unlikely that circadian fluctuations accounted for group differences.

The present data show no beneficial effect of a single cardiovascular exercise session compared with a single stretching and toning session on early stages of memory consolidation in young adults. However, acute cardiovascular exercise increased both BDNF and VEGF levels in comparison to non-cardiovascular exercise. Moreover, positive correlations between changes in BDNF and memory measures were compatible with the idea and previous findings (Skriver et al., 2014; Bosch et al., 2017b) that BDNF contributed to memory enhancement after acute cardiovascular exercise.

DATA AVAILABILITY STATEMENT

The raw data analyzed in this study are available on request from the corresponding author. The data are not publicly available due to privacy concerns.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Local Ethics Committee of the Faculty of Psychology and Human Movement Science, University of Hamburg. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LK contributed to the study concept and design, recruitment of participants, implementation, data management, data analysis, interpretation of results, and drafted the manuscript. A-MK contributed to the sports medical data collection, data management, data analysis, and to the critical review of the manuscript. K-MB and RR contributed to the study concept and critical review of the manuscript. TJ contributed to the study concept, analysis of BDNF and VEGF data and interpretation, and critical review of the manuscript. BR contributed to the study concept and design, interpretation of results, critical review of the manuscript, and secured funding for the study. KH contributed to the study concept and design, data analysis, interpretation of results, and critical review of the manuscript. All authors contributed to the article and approved the submitted version.

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Effects of Aerobic Exercise and Mind-Body Exercise in Parkinson's Disease: A Mixed-Treatment Comparison Analysis

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Background/Objectives: Aerobic exercise and mind-body exercise, are vital for improving motor and non-motor functional performance of Parkinson's disease (PD). However, evidence-based recommendations on which type of exercise is most suitable for each individual are still lacking. Therefore, we conduct a network meta-analysis to assess the relative efficacy of aerobic and mind-body exercise on motor function and non-motor symptoms in Parkinson's disease and to determine which of these therapies are the most suitable.

Design: A network meta-analysis and dose-response analysis.

Setting and Participants: Medline, Embase (all via Ovid), and the Cochrane Central Register of Controlled Trials were comprehensively searched for related trials through April 2021.

Measurements: Study quality was evaluated using the Cochrane Risk of Bias Tool. The effect sizes of continuous outcomes were calculated using mean differences (MDs) or standardized mean differences (SMDs). A network meta-analysis with a frequentist approach was conducted to estimate the efficacy and probability rankings of the therapies. The dose-response relationship was determined based on metaregression and SUCRA.

Results: Fifty-two trials with 1971 patients evaluating six different therapies were identified. For the UPDRS-motor score and TUG score, yoga all ranked highest (SUCRA = 92.8%, 92.6%, respectively). The SUCRA indicated that walking may best improve the BBS score (SUCRA = 90.2%). Depression, cognitive and activities of daily living scores were significantly improved by yoga (SUCRA: 86.3, 95.1, and 79.5%, respectively). In the dose-response analysis, 60-min sessions, two times a week might be the most suitable dose of yoga for reducing the UPDRS-motor score of PD patients.

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Conclusion: Yoga and walking are important options for increasing functional mobility and balance function, and yoga might be particularly effective for decreasing depressive symptoms and cognitive impairment and improving activities of daily living in PD. The potential optimal dose of yoga for enhancing motor ability in PD patients is 60-min sessions, two times a week.

Registration: PROSPERO CRD42021224823.

Keywords: aerobic exercises, mind-body exercise, Parkinson's disease, network meta-analysis, dose response

INTRODUCTION

According to epidemiological studies of Parkinson's disease (PD), the global PD population reached approximately 6,100,000 in 2016 (Collaborators, 2018, 2019), making it the second most common neurodegenerative disorder. PD affects the motor and non-motor systems, resulting in poor quality of life for patients and a heavy burden on families and society. There is no curative treatment for PD, which poses a great challenge for global health systems that needs to be resolved.

Although pharmacotherapy is currently still the first-line treatment, side effects and response fluctuations limit its application (Connolly and Lang, 2014; Ellis and Fell, 2017; Stoker and Barker, 2020). The latest guideline (Canadian guideline for Parkinson's disease) and studies have indicated that physical exercise, especially aerobic and mind-body exercise, are vital for improving motor and non-motor functional performance and delaying the progression of PD (Ahlskog, 2018; Schenkman et al., 2018; Grimes et al., 2019; van der Kolk et al., 2019; Deuel and Seeberger, 2020). Previous meta-analyses have demonstrated that these types of exercise may be beneficial for maintaining brain health, promoting functional mobility performance, psychosocial function and quality of life (Shu et al., 2014; Kwok et al., 2016; Chen et al., 2020; Schootemeijer et al., 2020). Moreover, these types of exercise might exert positive effect on cognitive function and wellbeing by enhancing cerebrovascular angiogenesis and regulating the brain plasticity (da Silva et al., 2018; Mandolesi et al., 2018; Pianta et al., 2019). However, aerobic exercise and mind-body exercise includes various types of exercise, such as treadmill exercise, walking, cycling, dance, tai chi and yoga. Combining different interventions when conducting a meta-analysis may induce confounding factors. Moreover, evidence-based recommendations on which type of exercise is most suitable for each individual are still lacking. Therefore, systematically determining the most effective treatment options for particular signs and symptoms from among all available types of aerobic exercise and mind-body exercise is critical to providing individual evidence-based recommendations for PD patients.

Network meta-analysis is a technique that uses direct and indirect results to compare multiple interventions simultaneously and estimates the rank order of the treatments, providing evidence-based recommendations for assisting medical decision making (Rouse et al., 2017; Dias and Caldwell, 2019). Therefore, in this study, we conducted a network meta-analysis to evaluate the effect of aerobic and mind-body exercise on motor function, functional mobility, psychosocial status and activities of daily living. Furthermore, we also explored the rankings of different exercise treatments and provided evidence-based recommendations for patients with PD under different situations.

MATERIALS AND METHODS

Study Registration

This network-meta analysis was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) with a record number CRD42021224823.

Search Strategy

The electronic databases Medline, Embase (all via Ovid), and the Cochrane Library were searched for all relevant citations published from inception through April 3, 2020. We used various combinations of medical subject headings and free terms, which included Parkinson's disease, aerobic and mind-body exercise (a list of relevant exercise interventions), and randomized clinical trial designs (search strategies are listed in **Supplementary 1**).

Selection and Exclusion Criteria

Eligible studies were included when they met the following criteria: (1). All studies were randomized controlled trials (RCTs). (2) The population of the included studies was adult patients diagnosed with PD. (3) Interventions contained at least one of the following exercises: treadmill exercise, walking, cycling, dance, yoga, and tai chi. The control group received usual care, was a waitlist control or performed other non-aerobic and non-mind-body exercise. (4) Outcomes of the studies included at least one of the following measurements: Unified Parkinson's Disease Rating Scale (UPDRS) score [UPDRS or Movement Disorder Society-Unified Parkinson's disease rating scale scores (MDS-UPDRS)], Berg Balance Scale (BBS) score, Timed-Up-and-Go (TUG) score, psychosocial outcomes (depressive scale: BDI, HADS-depression; cognitive functional scale: DRS, MMSE, MoCA, PDQ39-cognition, and UPDRS-mental) and activities of daily living (ADL) (UPDRS-ADL, PDQ39-ADL).

Studies were excluded if insufficient data or information concerning assessment was provided. We also excluded quasi-RCTs, animal trials, clinical protocols, conference abstracts, case reports and systematic reviews.

Data Extraction and Quality Assessment

Two investigators (YX & HG) independently extracted the relevant data and information from the eligible studies. Basic information about the study characteristics (first author, year, design), population, interventions and comparisons (duration, frequency, length), and measurement outcomes was extracted. Another two reviewers (CW & CT) evaluated the quality of the included studies based on the standard criteria of the Cochrane Risk of Bias Tool (Savovic et al., 2014). Any disagreements that existed were resolved through discussion. If necessary, a senior investigator (MZ) was consulted to achieve a consensus.

Outcomes

The outcomes of this network meta-analysis were listed as follow:

Primary Outcome

Motor outcomes: UPDRS-motor score [assessed by UPDRS III and MDS-UPDRS III, UPDRS III were converted to MDS-UPDRS III by adding 7 points according to the validated calibration method (Hentz et al., 2015)]; BBS and TUG outcomes.

Non-motor outcomes: Psychosocial outcomes (depressive and cognitive functional scale scores) and ADL.

Secondary Outcome

Safety outcomes: Non-serious and serious adverse events.

Statistical Analysis

We performed a pairwise meta-analysis first. All variables were continuous data and presented as mean with standard deviation (SD). Mean differences (MD = Absolute difference between the mean value in two groups, defined as the difference in means between treatment and control group and was calculated using the same scale) or standardized mean differences (SMD = Difference in mean outcome between groups/Standard deviation of outcome among participants, which was used to combine data when trials with different scale) with 95% confidence interval (CI) was reported as a continuous outcome (Borenstein et al., 2010; Cumpston et al., 2019). We assessed heterogeneity by testing the I^2 statistic. If statistically quantifiable heterogeneity existed, a random-effects model was fitted. Otherwise, we used a fixed-effect model (Borenstein et al., 2010).

Then, we conducted a network meta-analysis for each outcome using a frequentist approach and the netmeta command in Stata version 14 (Shim et al., 2017). We quantified potential inconsistencies between the direct and indirect results by using network side-split analysis and a design-by-treatment interaction model (Dias et al., 2010; White et al., 2012). If the p-value of the design-by-treatment interaction model and the network side-split analysis exceeded 5%, a consistency model was used to evaluate the effect size of the multiple treatment comparisons.

We estimated the ranking probabilities of each treatment for different outcomes based on the surface under the cumulative ranking curve (SUCRA) and mean ranking (Salanti et al., 2011). Moreover, to examine the stability of the result and evaluate whether the results were impacted by study characteristic, sensitivity analysis was conducted based on the baseline patient characteristics. We also explored the potential dose-response relationship using metaregression if the data of the included studies allowed it. To assess publication bias, we used the comparison-adjusted funnel plot to detect the risk of potential publication bias. If the effect size of the included studies was distributed symmetrically, which indicated that there was minimal publication bias in this network meta-analysis.

RESULTS

Study Identification and Selection

We retrieved a total of 5,919 publications from the electronic databases and eliminated 1,592 duplicate publications. A total of 4,327 publications were left for screening according to their titles and abstracts. Of those, 4,095 publications were removed, and 232 remaining publications were then identified as potentially eligible studies and underwent a full-text review. Finally, fifty-two relevant publications were included in the network meta-analysis (**Supplementary Figure 1**).

Characteristics of the Included Studies

A total of 52 eligible RCTs with 1,971 patients diagnosed with PD were included in this network meta-analysis. The interventions of the included trials mainly included treadmill exercise, walking, cycling, dance, yoga, and tai chi. Most trials used usual care, waitlist or other non-aerobic exercise as the control. The duration of each intervention varied from 20 to 90 min per session, and the frequency ranged from one to five times per week. Forty-two RCTs assessed motor function using the UPDRS-motor score. Fourteen studies used the BBS to assess balance function. Twenty-three studies evaluated mobility function using the TUG test, twelve RCTs assessed depressive outcomes, 13 RCTs evaluated cognition, and 17 studies reported ADL outcomes (see **Supplementary Table 1**).

Quality Assessment of the Included Studies

Among the 52 RCTs, 65.38% had a low risk in terms of random sequence generation, and 63.46% reported the use of allocation concealment methods. Few studies (11.54%) used blinding methods for participants and personnel because exercise is a non-pharmacologic treatment. Forty studies (77.36%) reported a low risk for bias in terms of blinding the outcome assessment. RCTs (84.62%) had a low risk of attrition bias. Forty-two studies reported a low risk of reporting bias. Overall, 67.31% were deemed to have a low risk of poor methodological quality, whereas 17 studies were regarded as having poor methodological quality (**Supplementary Figures 2,3**).

Analysis of Outcomes

Primary Outcomes

Motor Outcomes

Unified Parkinson's Disease Rating Scale-Motor. Forty-two RCTs with six different therapy categories assessed motor function using UPDRS III-motor measurements. Treadmill exercise contributed 18.8% to the network plot, walking 8.2%, cycling 4.7%, dance 9.4%, yoga 5.8%, tai chi 7%, and the control group 45.8% (**Supplementary Figure 4A**).

The pairwise meta-analysis illustrated that all therapies could decrease the overall UPDRS motor score. Those performing treadmill exercise, walking, dance, yoga, or tai chi all functioned better than those in the control group in terms of the UPDRS-motor score (**Figure 1A**).

Quantification of the inconsistencies between direct and indirect comparisons using node-splitting methods and the design-by-treatment interaction model showed that all p-values exceeded 0.05 (**Supplementary Table 2**), which indicated satisfactory consistency.

Network meta-analysis indicated that treadmill exercise [MD = −3.23,CI = (−4.80, −1.67)], walking [MD = −6.12, CI = (−8.62, −3.61)], dance [MD = −4.84, CI = (−7.45, −2.24)], yoga [MD = −8.07, CI = (−11.14, −5.00)], and tai chi [MD = −4.66, CI = (−7.10, −2.22)] were superior to the control in reducing the UPDRS-motor score. Yoga and walking were significantly more effective in decreasing UPDRS-motor scores than treadmill therapy (**Figure 2A**). The ranking probability of six different interventions illustrated that yoga (SUCRA:94.1%) ranked first for the UPDRS-motor score based on the SUCRA, followed by walking, dance, cycling, tai chi, and treadmill therapy (**Figures 3A–C**).

Dose-Response Analysis

Because yoga was ranked first for the UPDRS-motor score, we further analyzed the optimal dose of yoga therapy for improving motor function in PD patients. We analyzed the potential optimal time of yoga per session in UPDRS motor score. Our metaregression revealed that the effect size was not significantly increased with increasing yoga intervention time each session ($p = 0.15 > 0.05$, **Figure 4A**). The results showed that a duration of 60 min (each time) was the most suitable duration for reducing the UPDRS-motor score of PD patients (SUCRA: 98.2%, **Figures 4B–D**). Besides, the result also indicated that 2 times a week might be the most suitable frequency for reducing the UPDRS-motor score of PD patients (SUCRA: 98.2%, **Figures 4E–H**).

Timed-Up-and-Go Test. The network plot of TUG outcome was shown in **Supplementary Figure 4B**. And the pairwise meta-analysis showed that compared with the control, yoga and tai chi therapies significantly decreased the TUG score. Overall therapies could reduce the TUG score (**Figure 1B**).

The consistency tests between the direct and indirect effects all indicated that the p-value exceeded 0.05 (**Supplementary Table 2**).

We conducted a network meta-analysis of TUG outcomes, and the results illustrated that yoga (MD = −2.77, CI = −4.68, −0.86), tai chi (MD = −1.13, CI = −1.92, −0.34), and treadmill exercise (MD = −1.61, CI = −2.91, −0.30) were more beneficial in reducing the TUG score than the control (**Figure 2B**). Moreover, we evaluated the rankings of the various treatments based on TUG scores and found that yoga ranked the highest (SUCRA: 92.6%), followed by treadmill exercise, tai chi, walking, cycling and dance (**Figures 3D–F**).

Berge Balance Scale. Fourteen studies including six treatments were included in the network meta-analysis evaluating BBS outcomes (**Supplementary Figure 4C**). **Figure 1C** shows that therapies could enhance the overall balance ability of PD patients. Walking, dance, yoga, and tai chi were highly effective in increasing balance ability.

The comparisons indicated satisfactory consistency (all, $p > 0.05$, **Supplementary Table 2**). The network comparison revealed that walking (MD = 7.16, CI = (2.26, 12.07), dance [MD = 5.18, CI = (1.53, 8.83)], and tai chi [MD = 4.15, CI = (0.92, 7.38)] were superior to the control in improving the BBS score (**Figure 2C**). The SUCRA indicated that walking had the highest rank for the BBS score (SUCRA: 90.2%), followed by dance, tai chi, and yoga (**Figures 3G–I**).

Clustered Ranking Plot of the Network

We constructed a clustered ranking plot of the network (UPDRS-motor and TUG, UPDRS-motor and BBS, and TUG and BBS) to comprehensively evaluate the most suitable treatment for

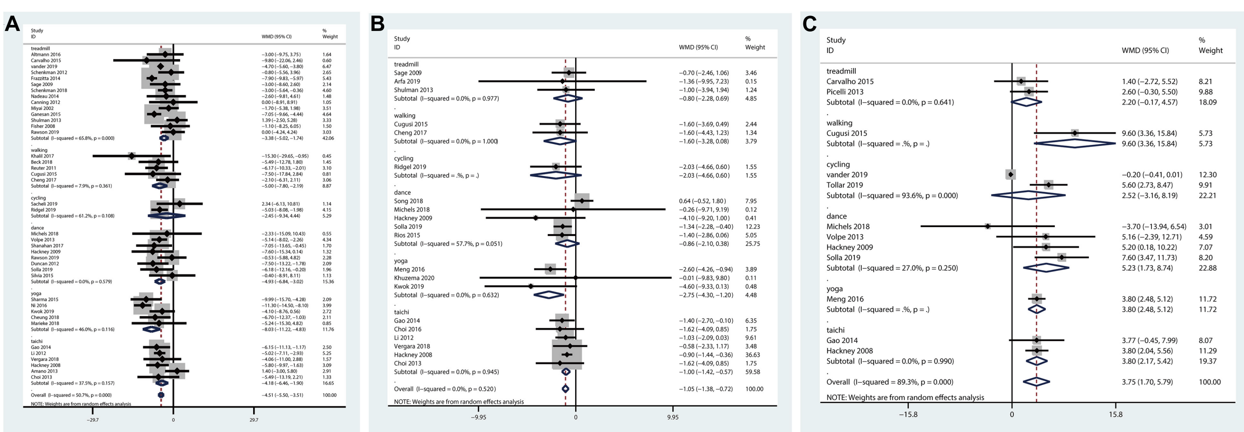

FIGURE 1 | Pairwise meta-analysis of aerobic and mind-body therapies on motor outcomes. **(A)** UPDRS-motor outcome. **(B)** TUG outcome. **(C)** BBS outcome. Meta-analysis results for pair-wise comparisons represented by MD and 95% credible interval (CrI).

A

yoga	1.52 (-2.47,5.51)	3.24 (-0.76,7.24)	3.93 (-0.07,7.93)	4.11 (-0.15,8.37)	**4.91 (1.45,8.38)**	**8.08 (5.02,11.13)**
-1.52 (-5.51,2.47)	walking	1.72 (-1.90,5.34)	2.41 (-1.25,6.06)	2.59 (-1.31,6.49)	**3.39 (0.83,5.96)**	**6.56 (3.97,9.14)**
-3.24 (-7.24,0.76)	-1.72 (-5.34,1.90)	dance	0.69 (-2.97,4.35)	0.87 (-3.07,4.82)	1.68 (-1.31,4.66)	**4.84 (2.25,7.43)**
-3.93 (-7.93,0.07)	-2.41 (-6.06,1.25)	-0.69 (-4.35,2.97)	taichi	0.18 (-3.77,4.14)	0.99 (-2.08,4.05)	**4.15 (1.56,6.73)**
-4.11 (-8.37,0.15)	-2.59 (-6.49,1.31)	-0.87 (-4.82,3.07)	-0.18 (-4.14,3.77)	cycling	0.80 (-2.50,4.10)	**3.96 (0.97,6.96)**
-4.91 (-8.38,-1.45)	**-3.39 (-5.96,-0.83)**	-1.68 (-4.66,1.31)	-0.99 (-4.05,2.08)	-0.80 (-4.10,2.50)	treadmill	**3.16 (1.51,4.82)**
-8.08 (-11.13,-5.02)	**-6.56 (-9.14,-3.97)**	**-4.84 (-7.43,-2.25)**	**-4.15 (-6.73,-1.56)**	**-3.96 (-6.96,-0.97)**	**-3.16 (-4.82,-1.51)**	control

B

yoga	1.16 (-1.15,3.48)	1.64 (-0.41,3.70)	1.62 (-0.75,4.00)	1.86 (-0.65,4.38)	1.96 (-0.19,4.11)	**2.77 (0.86,4.68)**
-1.16 (-3.48,1.15)	treadmill	0.48 (-1.05,2.01)	0.46 (-0.75,1.67)	0.70 (-0.59,1.99)	0.80 (-0.85,2.44)	**1.61 (0.30,2.91)**
-1.64 (-3.70,0.41)	-0.48 (-2.01,1.05)	taichi	-0.02 (-1.63,1.59)	0.22 (-1.59,2.03)	0.32 (-0.95,1.59)	**1.13 (0.34,1.92)**
-1.62 (-4.00,0.75)	-0.46 (-1.67,0.75)	0.02 (-1.59,1.63)	walking	0.24 (-1.42,1.90)	0.34 (-1.39,2.06)	1.15 (-0.28,2.57)
-1.86 (-4.38,0.65)	-0.70 (-1.99,0.59)	-0.22 (-2.03,1.59)	-0.24 (-1.90,1.42)	cycling	0.10 (-1.82,2.01)	0.91 (-0.74,2.55)
-1.96 (-4.11,0.19)	-0.80 (-2.44,0.85)	-0.32 (-1.59,0.95)	-0.34 (-2.06,1.39)	-0.10 (-2.01,1.82)	dance	0.81 (-0.19,1.81)
-2.77 (-4.68,-0.86)	**-1.61 (-2.91,-0.30)**	**-1.13 (-1.92,-0.34)**	-1.15 (-2.57,0.28)	-0.91 (-2.55,0.74)	-0.81 (-1.81,0.19)	control

C

walking	-1.98 (-8.14,4.17)	-3.02 (-8.88,2.85)	-3.89 (-10.09,2.32)	-4.47 (-8.98,0.04)	-5.06 (-10.85,0.74)	**-7.16 (-12.07,-2.26)**
1.98 (-4.17,8.14)	dance	-1.03 (-5.92,3.86)	-1.90 (-7.10,3.30)	-2.49 (-7.51,2.54)	-3.07 (-8.01,1.87)	**-5.18 (-8.83,-1.53)**
3.02 (-2.85,8.88)	1.03 (-3.86,5.92)	taichi	-0.87 (-5.31,3.57)	-1.46 (-6.17,3.26)	-2.04 (-6.56,2.48)	**-4.15 (-7.38,-0.92)**
3.89 (-2.32,10.09)	1.90 (-3.30,7.10)	0.87 (-3.57,5.31)	yoga	-0.59 (-5.69,4.51)	-1.17 (-6.16,3.82)	-3.28 (-7.04,0.48)
4.47 (-0.04,8.98)	2.49 (-2.54,7.51)	1.46 (-3.26,6.17)	0.59 (-4.51,5.69)	treadmill	-0.58 (-5.25,4.08)	-2.69 (-6.13,0.75)
5.06 (-0.74,10.85)	3.07 (-1.87,8.01)	2.04 (-2.48,6.56)	1.17 (-3.82,6.16)	0.58 (-4.08,5.25)	cycling	-2.11 (-5.30,1.08)
7.16 (2.26,12.07)	**5.18 (1.53,8.83)**	**4.15 (0.92,7.38)**	3.28 (-0.48,7.04)	2.69 (-0.75,6.13)	2.11 (-1.08,5.30)	control

FIGURE 2 | Network meta-analysis of the efficacy of exercise therapies on motor outcomes. **(A)** UPDRS-motor outcome. **(B)** TUG outcome. **(C)** BBS outcome. MD and 95% credible interval (CrI) estimations were calculated as column-defining interventions compared with row-defining interventions. Significant results were labeled with bold, red and underlined.

improving motor function in PD. The results showed that the yoga, walking, dance, and tai chi groups had higher SUCRA values in the clustered ranking plot, which indicated that yoga and walking in particular, in addition to dance and tai chi, are the most suitable therapies for increasing overall motor function in PD patients (**Figure 5**).

Non-motor Outcomes

Depression Scale. Twelve studies with five treatments assessed depression scales (**Supplementary Figure 4D**). The pairwise meta-analysis showed that treadmill and yoga therapy significantly decreased depressive symptoms in the PD group compared with the control group (**Supplementary Figure 5A**).

All *p*-values exceeded 0.05 in the network side-split model, which revealed that the direct and indirect comparison outcomes were consistent (**Supplementary Table 2**).

The network meta-analysis of five different exercises based on depression scale outcomes showed that yoga was more effective in decreasing depressive symptoms than the control [SMD = −0.88, CI (−1.64, −0.12)]. Yoga, treadmill exercise and dance were significantly superior to cycling for reducing depression scores. Yoga therapy (SUCRA: 86.3%) was ranked highest for ameliorating PD with depression, followed by walking, treadmill exercise and dance (**Supplementary Figures 6A, 7A** and **Supplementary Table 3**).

Cognitive Assessment. Thirteen studies with five interventions assessed cognitive function (**Supplementary Figure 4E**). The pairwise meta-analysis showed that only dance therapy was more effective in improving the cognition of PD patients than the control (**Supplementary Figure 5B**).

We found that all *p*-values of consistency tests were higher than 0.05, which indicated that direct and indirect effects had good consistency (**Supplementary Table 2**).

The results of the network meta-analysis showed that only yoga was associated with significantly higher cognitive function scores than the control [SMD = 1.32 (0.11, 2.54)].The ranks of the five interventions for enhancing cognitive function in PD were as follows: yoga, dance, treadmill exercise, walking, and cycling (**Supplementary Figures 6, 7B** and **Supplementary Table 3**).

Activities of Daily Living. Seventeen studies assessed ADL in PD. We conducted a pairwise meta and the results demonstrated that treadmill exercise, cycling and yoga were all associated with significantly greater changes in ADL scores than the control (**Supplementary Figure 5C**).

The *p*–values of consistency tests were substantially higher than 0.05, which demonstrated that the network analysis had good consistency (**Supplementary Table 2**).

We conducted a network meta-analysis to assess the intervention effects in terms of ADL. The results revealed that yoga, cycling, and treadmill exercise were all superior to the control in improving ADL [SMD = −0.60 (−1.00, −0.20); SMD = −0.53 (−0.97, −0.09); and SMD = −0.47 (−0.74, −0.19), respectively].

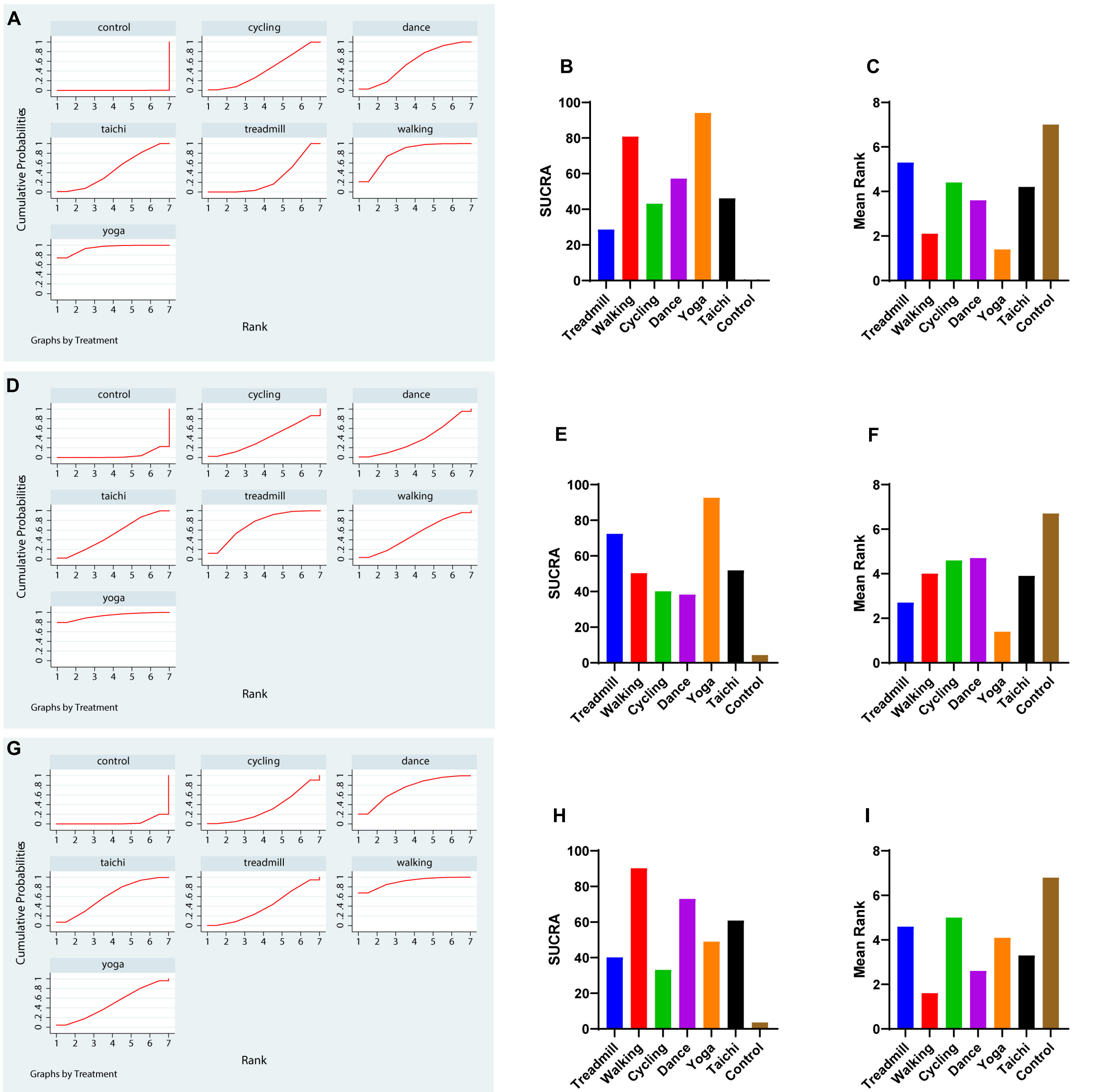

FIGURE 3 | The rank probability of various interventions based on the SUCRA. **(A–C)** Rank probability and mean rank on UPDRS-motor outcome. **(D–F)** TUG outcome. **(G–I)** BBS outcome. The greater the SUCRA value is, the better the rank.

Furthermore, yoga and treadmill therapy were significantly more effective in improving performance of activities of daily living than dance. The rankings of these five interventions, which were based on the SUCRAs for the ADL scores, showed that yoga ranked first, followed by cycling, treadmill exercise and tai chi (**Supplementary Figures 6C, 7C** and **Supplementary Table 3**).

Secondary Outcomes

Adverse Outcomes

Thirty-three studies reported adverse events related to exercise therapies. Among these RCTs, 21 studies reported that no adverse events occurred during treatment. The remaining studies reported a minimal number of adverse events, mainly knee, neck and back pain, muscle soreness and non-injurious falls. All these events and the symptoms were resolved by resting or simple treatment without further management (see **Supplementary Table 1**).

Sensitivity Analysis

In order to minimize the influence of heterogeneous baseline severity of PD in our study, we restricted our analysis into trials with early to-moderate stage of Parkinson's disease

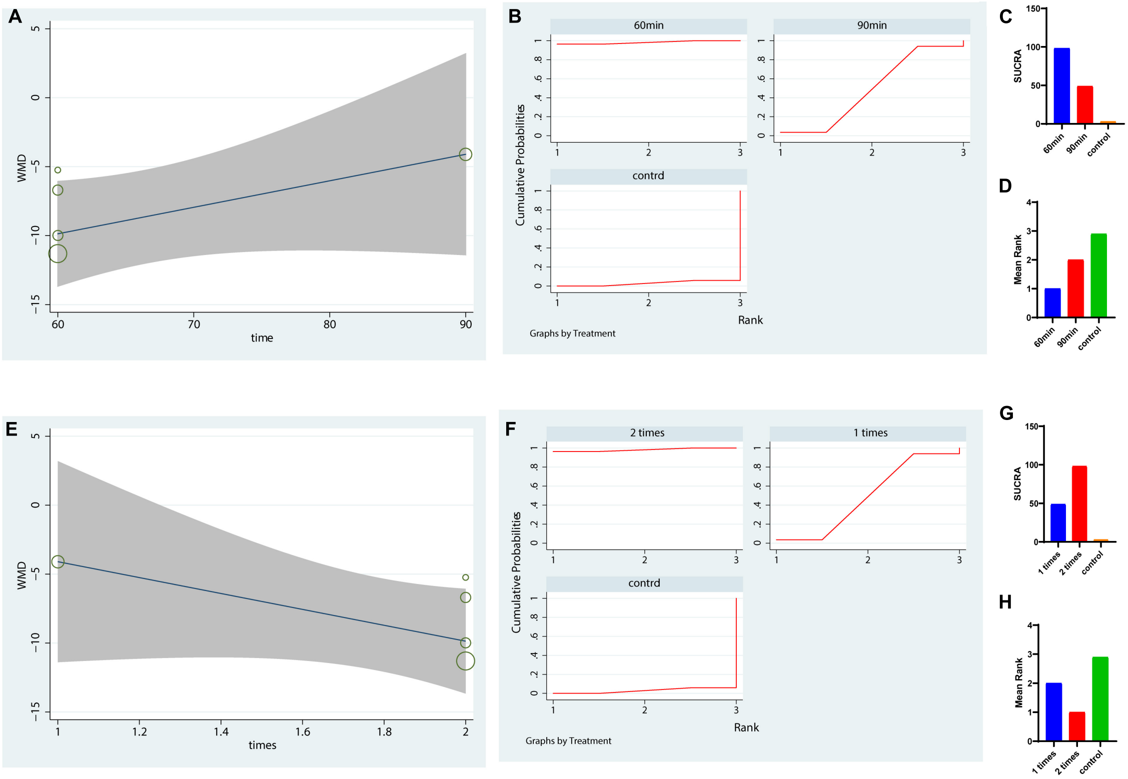

FIGURE 4 | Dose response of yoga using meta-regression and SUCRA on UPDRS-motor outcome. **(A–D)** The potential optimal time of yoga per session in UPDRS motor scale; **(E–H)** The potential optimal frequency of yoga each week in UPDRS motor outcome. **(A,E)** Dose-response curve for yoga using metaregression. **(B–D,F–H)** Dose response of yoga based on the rank probability and mean rank. The greater the SUCRA value is, the better the rank.

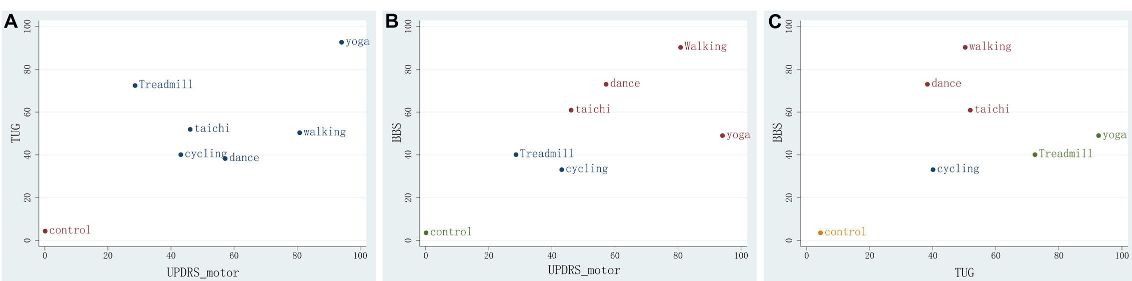

FIGURE 5 | Clustered ranking plot of the network. **(A)** For UPDRS-motor&TUG outcomes. **(B)** For UPDRS&BBS. **(C)** For TUG&BBS outcomes. The plots are based on cluster analyses of SUCRA values. Each plot shows the SUCRA values for two different outcomes. The therapies in the upper right corner are more effective than the other therapies.

as sensitivity analysis. The result showed that five therapies were superior to the control in reducing the UPDRS-motor score and yoga ranked first based on the SUCRA (93.4%). Besides, a sensitivity analysis after excluding studies that contained resistance active exercise as control group was conducted. All therapies except cycling were significantly superior to placebo and yoga also ranked first based on the SUCRA (95.2%), which were consistent with those previous produced (**Supplementary Figures 8A–H**). Besides, the sensitivity analysis of other outcomes (TUG, BBS, Depression scale, Cognitive outcome and ADL) were also in line with those previous conducted (the specific analysis were shown in **Supplementary Figures 8I–X** and **Supplementary Figures 9A–H**). The sensitivity analysis all indicated the results were stable.

Publication Bias

We constructed a funnel plot of our outcomes to assess publication bias. The plots all showed that the effect size of the included studies was distributed symmetrically, which demonstrated that there was minimal publication bias in this analysis (**Supplementary Figure 10**).

DISCUSSION

Principal Findings

We conducted a network meta-analysis that included 52 RCTs with six different treatments and obtained several principal findings summarized as follows.

The pooled results suggested that yoga, walking, dance, and tai chi were superior in reducing the UPDRS-motor scores of PD patients, and yoga and walking might be highly effective based on the SUCRA rankings. In the TUG test, yoga, tai chi and treadmill exercise were superior to the control. Additionally, yoga ranked first in decreasing the TUG score. Moreover, in terms of the BBS Walking had the highest efficacy among these various treatments in terms of BBS score. According to the clustered ranking plot of the network, yoga and walking might be the important therapies for comprehensively increasing motor and balance function in PD patients. Previous studies also found that yoga and walking exerted beneficial effects on motor function in PD (Bombieri et al., 2017; Cugusi et al., 2017; Godi et al., 2019; Adams et al., 2020; De Santis and Kaplan, 2020; Deuel and Seeberger, 2020).

Regarding psychosocial outcomes, the results suggested that yoga and dance could be significantly more effective in reducing depressive symptoms and improving cognitive function. Overall, yoga might be the important alternative therapy for PD patients with depression or dementia according to the SUCRA rankings. These findings were in line with previous studies revealing that patients report that yoga is enjoyable, feasible and beneficial regarding their depressive and anxiety symptoms (Jin et al., 2019; Deuel and Seeberger, 2020; Sagarwala and Nasrallah, 2020). In addition, a previous study demonstrated that yoga enhanced executive functions, memory and attention to some extent, which was consistent with our results (Chobe et al., 2020). Furthermore, dance might also be an important option that could be recommended for PD patients with cognitive impairment because the pairwise-meta result and previous studies all indicated that dance has potential benefit for ameliorating cognitive dysfunction (Kalyani et al., 2019; Hasan et al., 2021).

For the ADL scale, we found that yoga, cycling, and treadmills were more effective than controls in improving the ADL of PD patients, especially yoga, which ranked higher in the ADL assessment, suggesting that yoga might be the vital option for patients with poor activities of daily living. A previous review also agreed with our results and indicated that yoga therapy improved the PDQ-ADL score and mood of PD patients more than other therapies (Subramanian, 2017).

No severe adverse events occurred during exercise therapies. Only a few patients suffered muscle soreness or minor low back or knee pain. All these events can be resolved by resting and not affect the treatment process. Overall, aerobic or mind-body therapy is a safer treatment for addressing PD symptoms than other therapies.

With regard to the quality of the included RCTs, 67.31% were determined to be high-quality RCTs, which indicated that the pooled results were robust and reliable overall. However, the high risk of improper blinding of participants still existed in this analysis, which might decrease the strength of the evidence to a degree.

Findings in Relation to Previous Reviews

To our knowledge, this network meta-analysis is the first study to include all previously examined types of aerobic and mind-body exercise and to explore the rankings of various types of therapies for PD according to a comprehensive range of outcomes. Most of the previous meta-analyses focused on evaluating the efficacy of only one type of exercise for PD (Cugusi et al., 2017; Liu et al., 2019; Robinson et al., 2019; Carapellotti et al., 2020). However, head-to-head comparisons between various therapies are still lacking, making it difficult for patients to make optimal decisions. Previous reviews about aerobic exercise reported that aerobic exercise have beneficial effects in improving motor action, balance function in PD patients (Shu et al., 2014; Schootemeijer et al., 2020), which were agreed with our results of aerobic exercise. A review compared the efficacy of different kinds of mind-body exercise, including yoga, and tai chi, for motor outcomes, depressive symptoms and quality of life in PD and implied that mind-body exercise might have significant improvements in motor function, depressive symptoms and quality of life in Parkinson's disease, which was consistent with most of our results (Jin et al., 2019). Another review also investigated the effect of mind-body exercises (including yoga, taichi, and dance) on physiological outcomes for PD, the result indicated that mind-body exercises have moderate to large beneficial effects on motor function (Kwok et al., 2016). However, these studies did not examine all previously examined types of aerobic and mind-body exercise together that might prohibited accurate comparisons of the efficacy of aerobic and mind-body therapies for PD outcomes. Furthermore, the assessment of non-motor function, especially psychiatric symptoms, was not amply investigated in these studies. Therefore, our analysis comprehensively assesses the efficacy of all previously examined aerobic and mind-body exercises for treating PD and determines the important therapy for improving motor and non-motor outcomes in PD.

Implications for Clinical Practice

Overall, our results have several clinical implications. First, the results suggest that yoga and walking may be the important exercises for enhancing motor function and balance functional ability. Second, yoga as a mind-body exercise is a good option for PD complicated with depressive disorder and cognitive impairment. Moreover, yoga therapy for 60 min, two times a week can be recommended as the potential optimal dose for improving mobility in PD. Therefore, these evidence-based results could be recommended for PD patients and assist clinical doctors in making appropriate decisions.

Limitations

Our analysis has several limitations. In terms of non-motor outcomes, few studies and interventions were included in the analysis. Moreover, RCTs of head-to-head comparisons with other active therapies that included non-motor assessments were lacking, providing little direct evidence for overall or accurate evaluation of the efficacy of exercise therapies for non-motor symptoms (especially depressive symptoms and cognitive function) in PD. Besides, because of the limit number of yoga studies and the limitations of SUCRA, the results in this study should be interpreted with caution. Hence, more studies involving yoga are needed. In addition, most of the included studies lacked participant blinding because the exercise therapies were non-drug interventions. However, this could have resulted in bias for the intervention group.

CONCLUSION

The network meta-analysis reported herein indicates that aerobic and mind-body therapies significantly improve the motor function of PD patients at all stages. Yoga and walking could be prior to recommend for PD patients with motor symptoms and balance impairment. Yoga may also be the important option for decreasing depressive disorder and cognitive impairment and could be recommended as part of treatment for life style changes in patients with PD. The potential appropriate dose of yoga for enhancing motor ability in PD patients is 60-min sessions, 2 times a week.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

MZ and DC designed the study and revised the manuscript for important intellectual content. YX and HG acquired the data. CW and CT analyzed and interpreted the data. CW drafted the manuscript. All authors read and approved the final 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/fnagi.2021.739115/full#supplementary-material

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Bi-Anodal Transcranial Direct Current Stimulation Combined With Treadmill Walking Decreases Motor Cortical Activity in Young and Older Adults

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Background: Walking in the "real world" involves motor and cognitive processes. In relation to this, declines in both motor function and cognition contribute to age-related gait dysfunction. Transcranial direct current stimulation (tDCS) and treadmill walking (STW) have potential to improve gait, particularly during dual-task walking (DTW); walking whilst performing a cognitive task. Our aims were to analyze effects of combined anodal tDCS + STW intervention on cortical activity and gait during DTW.

Methods: Twenty-three young adults (YA) and 21 older adults (OA) were randomly allocated to active or sham tDCS stimulation groups. Participants performed 5-min of mixed treadmill walking (alternating 30 s bouts of STW and DTW) before and after a 20-min intervention of active or sham tDCS + STW. Anodal electrodes were placed over the left prefrontal cortex (PFC) and the vertex (Cz) using 9 cm^2 electrodes at 0.6 mA. Cortical activity of the PFC, primary motor cortex (M1), premotor cortex (PMC), and supplementary motor area (SMA) bilaterally were recorded using a functional near-infrared spectroscopy (fNIRS) system. Oxygenated hemoglobin (HbO_2) levels were analyzed as indicators of cortical activity. An accelerometer measured gait parameters. We calculated the difference between DTW and STW for HbO_2 and gait parameters. We applied linear mixed effects models which included age group (YA vs. OA), stimulation condition (sham vs. active), and time (pre- vs. post-intervention) as fixed effects. Treadmill belt speed was a covariate. Partial correlation tests were also performed.

Results: A main effect of age group was observed. OA displayed higher activity bilaterally in the PFC and M1, unilaterally in the right PMC and higher gait variability than YA. M1 activity decreased in both YA and OA following active tDCS + STW. There was no overall effect of tDCS + STW on PFC activity or gait parameters. However, negative correlations were observed between changes in left PFC and stride length variability following active tDCS + STW intervention.

Conclusion: Increased activity in multiple cortical areas during DTW in OA may act as a compensatory mechanism. Reduction in M1 activity following active tDCS + STW with no observed gait changes suggests improved neural efficiency.

Keywords: non-invasive brain stimulation, functional near-infrared spectroscopy, locomotion, cognition, ageing

INTRODUCTION

Walking ability is a sensitive indicator of health status in older adults (OA) (Studenski et al., 2011; Morris et al., 2016). Gait dysfunction is common in OA which decreases independence, heightens falls risk (Lord et al., 1996; Hausdorff et al., 2001; Verghese et al., 2009), increases health care costs (Heinrich et al., 2009), and results in an overall decreased quality of life (Lin et al., 2015). Age-related gait changes linked with increased falls risk include reduced gait speed and step length, and increased gait variability in comparison to young adults (YA) (Hausdorff et al., 2001; Verghese et al., 2009; Sawa et al., 2014; Aboutorabi et al., 2016). These gait parameters have also been associated with deficits in cognitive parameters such as executive function and attention in OA and are a potential indicator of cognitive impairment (Yogev-Seligmann et al., 2008; Morris et al., 2016). The interplay between cognition and gait is frequently assessed in the laboratory with a dual-task walking (DTW) paradigm: walking whilst simultaneously conducting a cognitive task. DTW attempts to replicate features of "real world" walking when a person walks whilst performing additional tasks. Age-related gait impairments have been reported to be more pronounced during DTW, referred to as cognitive-motor interference [i.e., difference between DTW and single-task walking (STW)] (Al-Yahya et al., 2011; Plummer-D'Amato et al., 2012). These findings emphasize the need to investigate strategies for gait rehabilitation in OA during DTW.

Physical training may improve mobility, cognition and promote functional and structural brain adaptations (Steinberg et al., 2018; El-Sayes et al., 2019). Additional interventions, such as transcranial direct current stimulation (tDCS), may also enhance mobility and cognition (Fregni et al., 2005; Javadi and Walsh, 2012; Zhou et al., 2014; Hurley and Machado, 2018; Manor et al., 2018; Steinberg et al., 2018). tDCS is a low-cost method of non-invasive brain stimulation involving the application of low-amplitude currents over cortical regions of interest to modulate cortical excitability, but insufficient to generate action potentials (Nitsche and Paulus, 2000; Nitsche et al., 2008). Briefly, a direct current device delivers low current (0.5–2 mA) through anodal (positive) and cathodal (negative) electrodes placed at specific locations on the scalp (Nitsche et al., 2008; Brunoni et al., 2012; Hurley and Machado, 2018). Anodal tDCS results in depolarization and cathodal tDCS in hyperpolarization of resting membrane potential, leading to increased neuronal excitability or reduced neuronal excitability, respectively (Nitsche and Paulus, 2000; Nitsche et al., 2008; Hurley and Machado, 2018). Previous studies have shown that anodal tDCS causes enhancement of neural activity, which can result in improvement of motor control and cognitive function (Fregni et al., 2005; Nitsche et al., 2008; Brunoni et al., 2012; Hurley and Machado, 2018; Manor et al., 2018). Since physical training and anodal tDCS can each independently improve gait and cognitive performance, applying both simultaneously may enhance outcomes and prolong effects (Fregni et al., 2005; Steinberg et al., 2018). Studies have demonstrated that acute physical training combined with anodal tDCS beneficially modifies gait parameters and cognition (Kaski et al., 2014b,a; Park et al., 2015; Manenti et al., 2016; Ishikuro et al., 2018). However, recent reviews of the literature (de Paz et al., 2019; Beretta et al., 2020) on the efficacy of combining physical training with anodal tDCS on gait were inconclusive. For example, a total of seven studies (Costa-Ribeiro et al., 2016, 2017; Kumru et al., 2016; Manenti et al., 2016; Fernández-Lago et al., 2017; Seo et al., 2017; Yotnuengnit et al., 2018) did not observe an improvement in walking performance after physical training combined with tDCS in patients with neurological disorders. The interpretation of such studies is limited by the fact that most previous studies applied tDCS over a single cortical area, typically either over the primary motor cortex (M1) or prefrontal cortex (PFC) (de Paz et al., 2019; Beretta et al., 2020). The efficacy of tDCS combined with physical training in gait rehabilitation therefore remains uncertain.

M1 and PFC play an important and specific role during walking. M1 is involved in the execution of movements (control of lower limb and trunk muscles) related to walking (Petersen et al., 2001, 2012), whilst the PFC has a modulatory function in the allocation of attention during gait (Koenraadt et al., 2014). In addition, M1 is the main contributor to the direct locomotor pathway, which is activated in the absence of pathologies or challenging situations (la Fougère et al., 2010; Herold et al., 2017). PFC is involved in the indirect locomotor pathway, which contributes more to gait control when the direct locomotor pathway is impaired, even during single-task walking (STW) (la Fougère et al., 2010; Herold et al., 2017). Studies assessing cortical activity using functional near-infrared spectroscopy (fNIRS) during different walking tasks provide evidence for the different roles of M1 and PFC. Previous studies have demonstrated that OA have higher prefrontal cortex (PFC) activity during STW compared to YA (Herold et al., 2017; Vitorio et al., 2017; Stuart et al., 2018; Pelicioni et al., 2019; Nóbrega-Sousa et al., 2020), which is increased during DTW (Herold et al., 2017; Vitorio et al., 2017; Stuart et al., 2018; Pelicioni et al., 2019; Nóbrega-Sousa et al., 2020). The increased PFC activity is theorized to be a cognitive compensation for age-related deficits (Cabeza et al., 2002; Bierre et al., 2017; Machado, 2021), recruiting additional cognitive resources, such as increased attention, during walking (Cabeza et al., 2002). Previous studies have indicated that increased M1 activity improves gait parameters (Koganemaru et al., 2018) and increased PFC activity improves cognitive function (Yanagisawa et al., 2010; Byun et al., 2014; Ji et al., 2019). Thus, M1 stimulation may facilitate the movement execution and PFC stimulation may promote greater cognitive resources for the task, which suggests that stimulation of both cortical areas may improve DTW performance.

In this study, we aimed to analyze the effect of a combined anodal tDCS (M1 and PFC stimulation) and treadmill walking intervention (tDCS + STW) on cortical activity (as measured by fNIRS) and gait parameters during DTW in YA and OA. As anodal tDCS is considered to increase excitability and facilitate the functional activation of M1 and PFC (Nitsche and Paulus, 2000), we hypothesized that activity in these areas would increase in both age groups during DTW following the anodal tDCS + STW intervention, but no such increases would occur in the control groups (following sham tDCS + STW). We also expected treadmill gait parameters during DTW in both OA and YA to improve (e.g., reduced gait variability) following the active tDCS + STW intervention but not in the control groups (following sham tDCS + STW), with greater benefits in OA, due to this group having greater gait impairments (Hausdorff et al., 2008; Yogev-Seligmann et al., 2008; Beurskens and Bock, 2012).

MATERIALS AND METHODS

This study used a double-blinded, randomized, and sham-controlled design. Ethical approval was granted by Newcastle University (ref. 6770/2018). We performed a power analysis, using data from a previous study investigating age-related differences in cortical activity, to determine the sample size of 7 necessary to detect a difference in HbO_2 of 12% with a standard deviation of 7% and power of 0.8 (Vitorio et al., 2018). An increase of over 38% in HbO_2 levels in the PFC has previously been reported following the application of single anodal tDCS to the PFC (da Conceição et al., 2021). A minimum sample size of 7 per group is therefore sufficient to detect anticipated changes in HbO_2 following administration of tDCS.

Forty-four participants were recruited and assigned into two groups: healthy young adults (YA; $n = 23$) and healthy older adults (OA; $n = 21$). Prior to the experiment, OA and YA were randomly allocated to active tDCS intervention (active-OA and active-YA) or sham tDCS intervention (sham-OA and sham-YA) (**Figure 1**). The inclusion criteria were YA aged between 18–40 years and OA aged ≥60 years, able to walk unaided for 5-min and good English language comprehension. Exclusion criteria included cognitive impairment [Montreal Cognitive Assessment (MoCA) score ≤ 21], psychiatric co-morbidities, history of drug or alcohol abuse, chronic musculoskeletal, cardiovascular or respiratory disease affecting gait, implanted metal objects, and a history of seizures or any contraindication to tDCS. This study was conducted according to the declaration of Helsinki and all participants signed an informed consent form prior to testing.

Study Design

Demographic characteristics and cognitive status were obtained for all participants at the beginning of the experiment. The MoCA was used to determine global cognitive function (Nasreddine et al., 2005). Fear of falling was assessed with the Falls Efficacy Scale - International (FES-I) score (Yardley et al., 2005). Participants also reported how many hours a week they exercised.

Participants performed two bouts of 5-min mixed treadmill walking before and after 20-min of tDCS + STW at self-selected speeds. We used the block design, adhering to previous recommendations for fNIRS studies (Herold et al., 2017; Vitorio et al., 2017). The 5-min mixed treadmill walking consisted of 10 trials of alternating 30 s STW and 30 s DTW bouts. The self-selected treadmill speed was maintained during the entire experiment and was determined by increasing belt speed until it was faster than the participants' preferred speed, then reducing belt speed until preferred speed was achieved (Vitorio et al., 2018). This was conducted whilst participants were blinded to their walking speed. DTW consisted of a digit vigilance task, which required participants to walk while listening to random numbers (from 1 to 9) played over a loudspeaker for 30 s. The intervals between numbers were randomized to prevent gait synchronization. Following cessation of the numbers, participants stated how many odd or even numbers they had heard. Speech was minimized to prevent motion artifact contaminating the fNIRS signals. Immediately before walking commenced, participants were given the class of numbers (odd or even) they were required to count. The performance in the cognitive digit vigilance task was quantified by the absolute error (difference between the correct answer and the response given by the participant) and expressed in percentage (0% indicates that there is no error).

Transcranial Direct Current Stimulation and Treadmill Walking Intervention

The experimental setup is summarized in **Figure 2**. Participants performed a total of 20-min of single-task treadmill walking at self-selected speed combined with anodal tDCS. Only the experimenter that applied the tDCS was aware of the intervention allocation of the individual (active or sham) to ensure both the participant and other experimenters were blinded. The active group received anodal tDCS over Cz (i.e., the vertex, which overlies M1) and the left PFC, between AF3 to Fp1 (9 cm anterior and 3 cm lateral to Cz), on the 10/20 EEG system, using a 3×3 cm^2 electrode. The cathode (5×5 cm^2) was positioned over the right mastoid, contralateral to the left PFC (**Figure 2A**). We selected the left PFC because tDCS applied to this area acutely was observed to improve both cognitive (Andrews et al., 2011; Chrysikou et al., 2013; Vanderhasselt et al., 2013) and motor functions (Wrightson et al., 2015; Manor et al., 2018;

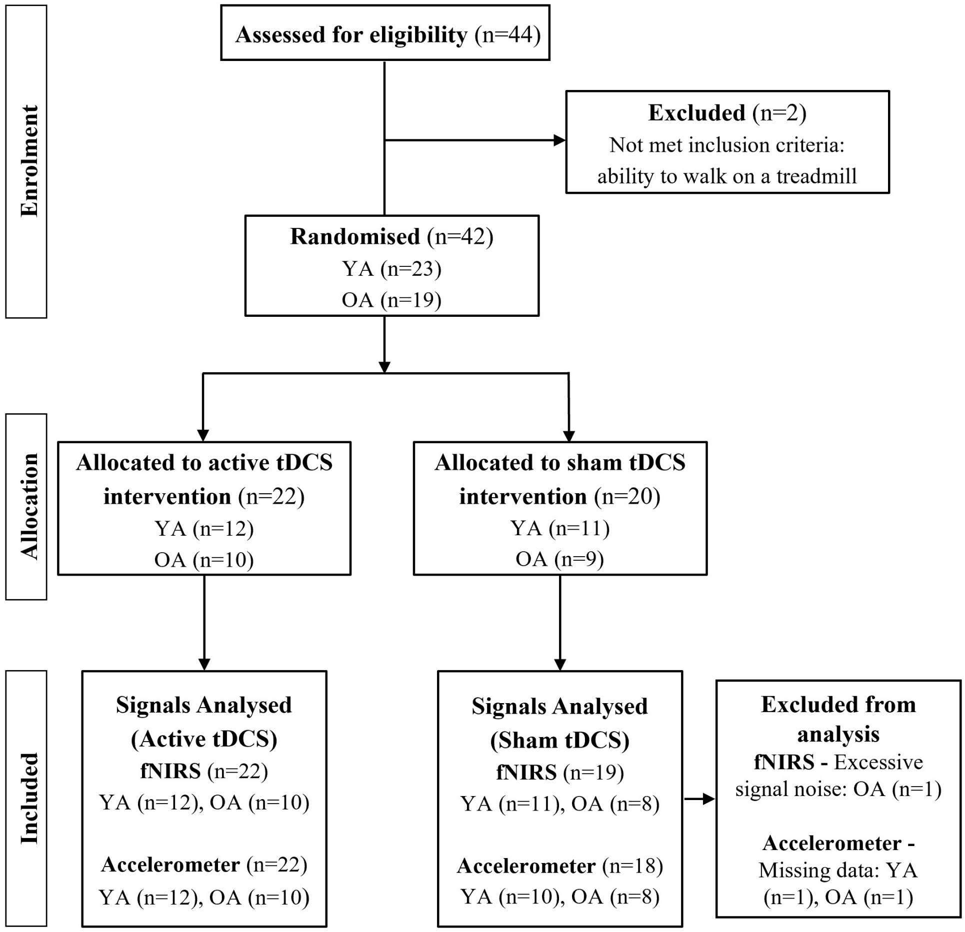

FIGURE 1 | Participant recruitment flowchart. YA: young adults; OA: older adults; tDCS: transcranial direct current stimulation; fNIRS: functional near-infrared spectroscopy.

Schneider et al., 2021). tDCS was applied using a battery-driven constant current stimulator (HDCStim, Newronika, Italy) with conductive paste to affix the electrodes to the scalp. tDCS was delivered at 0.6 mA for 20-min with a ramp-up of 10 s. We chose 0.6 mA because we used small tDCS electrodes (area 9 cm^2). Thus, we decreased the intensity of the current to ensure that the current density (current strength divided by electrode size) was maintained at 0.067 mA/cm^2, within the recommended safety limits (0.029–0.08 mA/cm^2) (Nitsche et al., 2008). In the sham stimulation, the tDCS montage was the same, but the current ramped down 10 s after the beginning of stimulation. This procedure provided a similar sensation of active stimulation but did not induce neurophysiological changes (Nitsche et al., 2008). At the end of the experiment, the participants completed an adverse events questionnaire to monitor differences in the perception of the stimulation experienced during active and sham tDCS (Brunoni et al., 2011). The rating of perceived exertion scale (Borg scale) was applied at the beginning, middle and end of the intervention period (0, 10, and 20 min, respectively) to measure the participant's effort and exertion.

Functional Near-Infrared Spectroscopy Recordings and Processing

After tDCS positioning, a headcap with fNIRS optodes was positioned on the participants' head. Both the fNIRS system and tDCS electrodes remained in place during the entire experimental protocol. We did not remove the fNIRS system during the intervention to ensure the consistency in the brain regions sampled pre- and post-intervention. Changes in oxygenated (HbO_2) and deoxygenated hemoglobin (HHb) were recorded with a sampling frequency of 22.2 Hz using a tethered fNIRS optical imaging system (LABNIRS; Shimadzu, Kyoto, Japan), with continuous wave laser diodes with wavelengths of 780, 805, 830 nm. The optical density of the raw signal was converted into HbO_2 and HHb using a modified Beer-Lambert Law. A 45-channel arrangement with 24 fiber optic optodes, consisting of 12 transmitters and 12 detectors, covered both hemispheres of the frontal lobe (**Figures 2B–C**). Emitter-detector distance was 30 mm. Participants wore a custom-made whole-head optode holder marked according to the international 10–20 EEG System (**Figure 2B**). A digitizer (FASTRAK, Polhemus, VT,

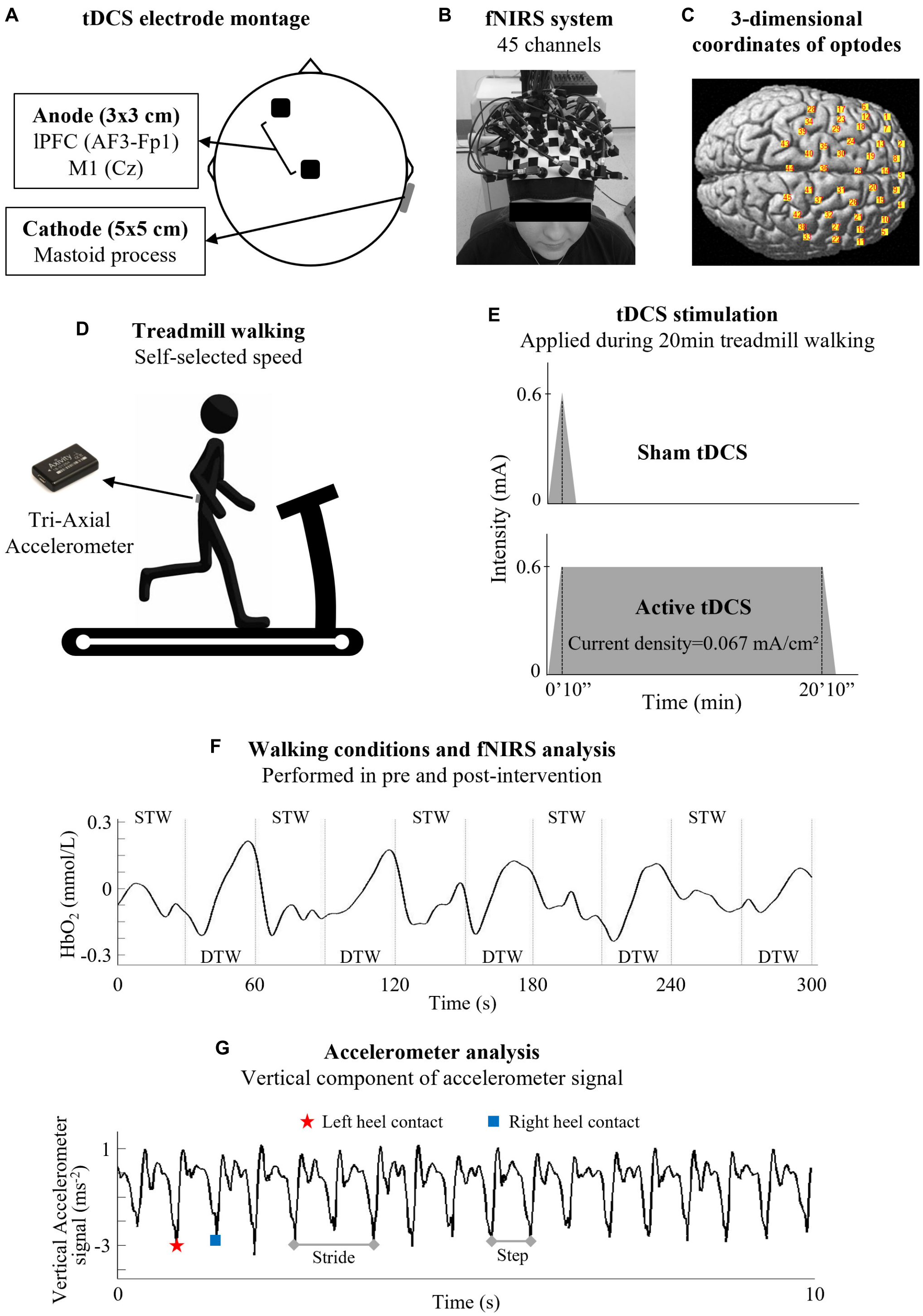

FIGURE 2 | Experimental setup. **(A)** Transcranial direct current stimulation (tDCS) was positioned over the left prefrontal cortex (lPFC) and Cz (i.e., the vertex, which overlies the primary motor cortex - M1), following the 10/20 EEG system. After tDCS positioning, **(B)** a headcap with fNIRS optodes was positioned on the participants' head. **(C)** Spatial registration of the 45-channels was calculated using a digitizer (FASTRAK) to confirm the optode position. **(D)** A tri-axial accelerometer was positioned over the 5th lumbar vertebra. Then, participants performed two bouts of 5-min mixed treadmill walking before and after 20-min treadmill walking combined with tDCS protocol. **(E)** Participants were randomly allocated to active tDCS intervention and received a 0.6 mA stimulation for 20-min, or sham tDCS intervention, and received a 0.6 mA stimulation for only 10 s. **(F)** The 5-min mixed treadmill walking consisted of 10 trials of alternating 30 s for both single task walking (STW) and dual task walking (DTW) bouts. HbO_2 concentration from the STW was subtracted from the DTW to evaluate the relative change in HbO_2 concentration ($\Delta_{DTW-STW}$). **(G)** Gait cycles were calculated using the accelerometer and the cognitive-motor interference was also calculated (difference between DTW and STW).

TABLE 1 | Participant characteristics (Mean ± SD).

	Older adults		Young adults	
	Active (*n* = 10)	**Sham (*n* = 9)**	**Active (*n* = 12)**	**Sham (*n* = 11)**
Age (years)*	66.0 ± 6.3	69.9 ± 4.8	19.3 ± 1.1	20.9 ± 4.2
Male/Female	5/5	2/7	1/11	2/9
Height (cm)	171.6 ± 10.7	167.7 ± 11.3	167.6 ± 7.7	174.4 ± 9.7
Body mass (kg)*	71.0 ± 9.4	73.6 ± 8.3	62.8 ± 10.0	65.89 ± 11.9
Education (years)	16.9 ± 2.9	15.7 ± 4.0	15.2 ± 1.0	16.3 ± 2.4
MoCA (0–30)	28.2 ± 1.1	28.3 ± 1.6	28.4 ± 2.1	28.8 ± 1.4
FES-I (16–64)	17.6 ± 1.2	18.1 ± 0.9	18.5 ± 2.1	18.6 ± 3.0
Exercise (hours/week)	8.2 ± 5.6	11.2 ± 5.9	7.3 ± 4.0	6.3 ± 6.5
Treadmill Speed (Km/h)*	2.9 ± 0.8	2.5 ± 1.0	4.0 ± 0.4	3.7 ± 0.7
AE Questionnaire (10–40)*	10.5 ± 0.7	10.7 ± 1.3	13.4 ± 1.7	13.7 ± 4.3

*MoCA, Montreal Cognitive Assessment; FES-I, Falls Efficacy Scale International; AE Questionnaire, Adverse Events Questionnaire. *: Significant effect of Age Group $p < 0.05$.*

United States) was used to register 3-dimensional coordinates of optodes and stimulation sites relative to landmarks (nasion, Cz, left and right pre-auricular points). The spatial registration was calculated using the free software package NIRS-SPM (Ye et al., 2009), which allows registration of fNIRS channel data onto the Montreal Neurological Institute standard space (Tsuzuki and Dan, 2014; **Figure 2C**). The brain regions of interest (ROI) measured included PFC (Brodmann areas 8, 9, 10, 45, and 46), PMC (Brodmann area 6, lateral), SMA (Brodmann area 6, medial), and M1 (Brodmann area 4) (Vitorio et al., 2018).

Processing of fNIRS followed previous recommendations (Vitorio et al., 2017). We selected the HbO_2 concentration as it is the most sensitive indicator of walking-related changes in cortical activity (Suzuki et al., 2004; Harada et al., 2009). The fNIRS data were pre-processed using NIRS-SPM open source toolbox for MATLAB (Ye et al., 2009). A low-pass filter (cut-off 0.14 Hz) based on a canonical hemodynamic response function was used to reduce the high-frequency noise (Friston et al., 2000). A wavelet-minimum description length detrending algorithm was applied to decompose NIRS measurements into global trends, hemodynamic signals, and uncorrelated noise components as distinct scales (Jang et al., 2009). Pre-processed data were exported to MATLAB (MATLAB and Statistics Toolbox Release 2015a, The MathWorks, Inc., Natick, MA, United States), in which further data processing was performed using customized scripts. Firstly, HbO_2 concentration signals were averaged per ROI (right and left PFC, PMC, SMA, and M1) and normalized by dividing them by corresponding signal amplitude (from minimum to maximum) value during the mixed treadmill walking (Koenraadt et al., 2014; Vitorio et al., 2018; Orcioli-Silva et al., 2020, 2021). Then, data were divided into two phases (**Figure 2F**): (i) a period running from 5 to 25 s of STW and (ii) a period running from 5 to 25 s of DTW. The initial 5 s and final 5 s of the tasks were removed due to the hemodynamic response phase lag (Vitorio et al., 2018). Subsequently, the normalized HbO_2 concentration was averaged (in time) over the STW (20 s) and DTW periods (20 s) for each ROI and each trial. Normalized HbO_2 concentration from STW was subtracted from the DTW to evaluate the relative change in HbO_2 concentration ($\Delta_{DTW-STW}$) (Maidan et al., 2016; Mirelman et al., 2017; Vitorio et al., 2018; Nóbrega-Sousa et al., 2020; Orcioli-Silva et al., 2020, 2021). The fNIRS outcome measure, ΔHbO_2, therefore represents the change in cortical activity during DTW compared to STW.

Gait Parameters Recordings and Processing

A tri-axial accelerometer (Axivity Ltd., Newcastle upon Tyne, United Kingdom), sampling at 100 Hz, positioned over the 5th lumbar vertebra, recorded trunk acceleration during the 5-min mixed treadmill walking before and after the intervention (**Figure 2D**). Gait parameters were extracted from the accelerometry data using previously validated algorithms (Del Din et al., 2016). Briefly, acceleration data were transformed to a horizontal-vertical coordinate system (Moe-Nilssen, 1998) and filtered with a fourth-order Butterworth filter (20 Hz) (Zijlstra and Hof, 2003; McCamley et al., 2012). Initial and final contact events within the gait cycle were estimated with a continuous wavelet transform (CWT) of the vertical acceleration which was first integrated and then differentiated using a Gaussian CWT. The initial and final contact events were detected as the local minima and maxima of the CWT, respectively (Del Din et al., 2016; **Figure 2G**). Both right and left heel strike were identified. Initial contact and final contact detection times were used to estimate the step, stance time (Del Din et al., 2016). Step/stride length was determined from the initial contact events through application of the inverted pendulum model described by Zijlstra and Hof (2003). We chose gait parameters that have been previously related to falls, such as the stance time ratio (Verghese et al., 2009), cadence (Lord et al., 1996), stride time variability (Hausdorff et al., 2001), and stride length variability (Verghese et al., 2009). We calculated the gait variability using the standard deviation from all steps (Del Din et al., 2016). Stance time ratio, also referred to as duty factor, is the ratio between the foot contact time and the stride time (Voigt et al., 2019). This parameter

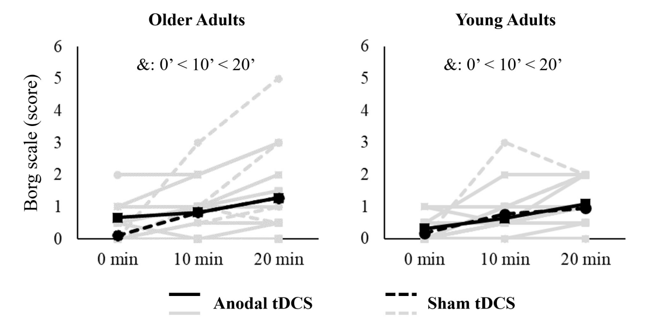

FIGURE 3 | Individuals (light gray lines) and means data (black lines) of perceived exertion scale (Borg) applied during 20-min treadmill walking combined with tDCS. &: indicates a main effect of intervention duration.

has important links to motor control system dynamics as well as to muscle metabolic energy expenditure (Beck et al., 2020). Gait speed was a covariate because we used a fixed treadmill speed for each individual. The difference between DTW and STW ($\Delta_{DTW-STW}$) for these selected gait parameters, which represents the cognitive-motor interference, was also calculated (Al-Yahya et al., 2011).

Statistical Analysis

Statistical analysis was performed using SPSS (v22, IBM, Armonk, NY, United States) for Windows. The level of significance was set at $p \leq 0.05$. Characterization data were analyzed using two-way ANOVAs with age group (YA and OA) and stimulation condition (active vs. sham tDCS) as independent variables. Chi-square test was applied to compare difference in sex between age groups or stimulation condition. The Borg scale was analyzed using linear mixed effects models with age group, stimulation condition, intervention duration (0, 10, and 20 min), and interactions as fixed effects. Differences in DTW related changes in gait, HbO_2 per ROI, and cognitive task were analyzed using linear mixed effects models. Fixed effects included were age group, stimulation condition, and time (pre- vs. post-intervention) with treadmill speed as a covariate. *Post hoc* tests with Bonferroni adjustment were used to localize the differences in significant main effects or interactions. Partial correlation tests were calculated separately for active and sham groups to explore the associations between gait parameters and cortical activity in response to intervention ($\Delta_{POST-PRE}$), while controlling for treadmill velocity and age. The partial eta-squared (η^2_p: 0.01 = small, 0.06 = moderate, 0.14 = large) and Cohen's *d* (*d*: 0.2 = small, 0.5 = moderate, 0.8 = large) statistic provided estimates of the effect sizes.

RESULTS

The characteristics of the participants are summarized in **Table 1**. The two-way ANOVA revealed a main effect of age group for body mass [$F_{(1,38)} = 27.37$, $p = 0.045$, $\eta^2_p = 0.113$], preferred treadmill speed [$F_{(1,38)} = 27.37$, $p < 0.001$, $\eta^2_p = 0.419$] and the Adverse Effects of tDCS Questionnaire [$F_{(1,38)} = 16.05$,

TABLE 2 | Means and standard deviation of dual task interference on gait parameters ($\Delta_{DTW-STW}$) and cognitive task error for pre- and post-intervention.

Variables	Older adults				Young adults			
	Active tDCS (*n* = 10)		Sham tDCS (*n* = 8)		Active tDCS (*n* = 12)		Sham tDCS (*n* = 11)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Cadence (step/min)	−0.08 ± 3.24	1.64 ± 1.68	−0.30 ± 3.50	0.92 ± 1.16	−0.01 ± 2.42	0.13 ± 0.85	0.22 ± 0.88	0.64 ± 1.00
Stance time ratio[a]	−0.002 ± 0.004	0.004 ± 0.009	−0.006 ± 0.012	0.000 ± 0.007	−0.001 ± 0.007	−0.002 ± 0.003	0.001 ± 0.003	0.000 ± 0.002
Stride time variability (s)	0.024 ± 0.034	−0.010 ± 0.020	0.050 ± 0.048	0.010 ± 0.040	−0.005 ± 0.064	−0.003 ± 0.004	0.001 ± 0.007	0.001 ± 0.018
Stride length variability (s)	−0.011 ± 0.012	0.005 ± 0.021	0.004 ± 0.021	0.007 ± 0.018	−0.023 ± 0.025	−0.013 ± 0.019	−0.012 ± 0.014	−0.012 ± 0.016
Cognitive task errors (%)[b]	3.53 ± 4.07	3.98 ± 5.78	4.32 ± 5.10	3.68 ± 7.35	4.15 ± 4.69	1.05 ± 1.60	4.58 ± 7.25	2.93 ± 5.51

[a]*Ratio between the foot contact time and the stride time.* [b]*Digit vigilance task.*

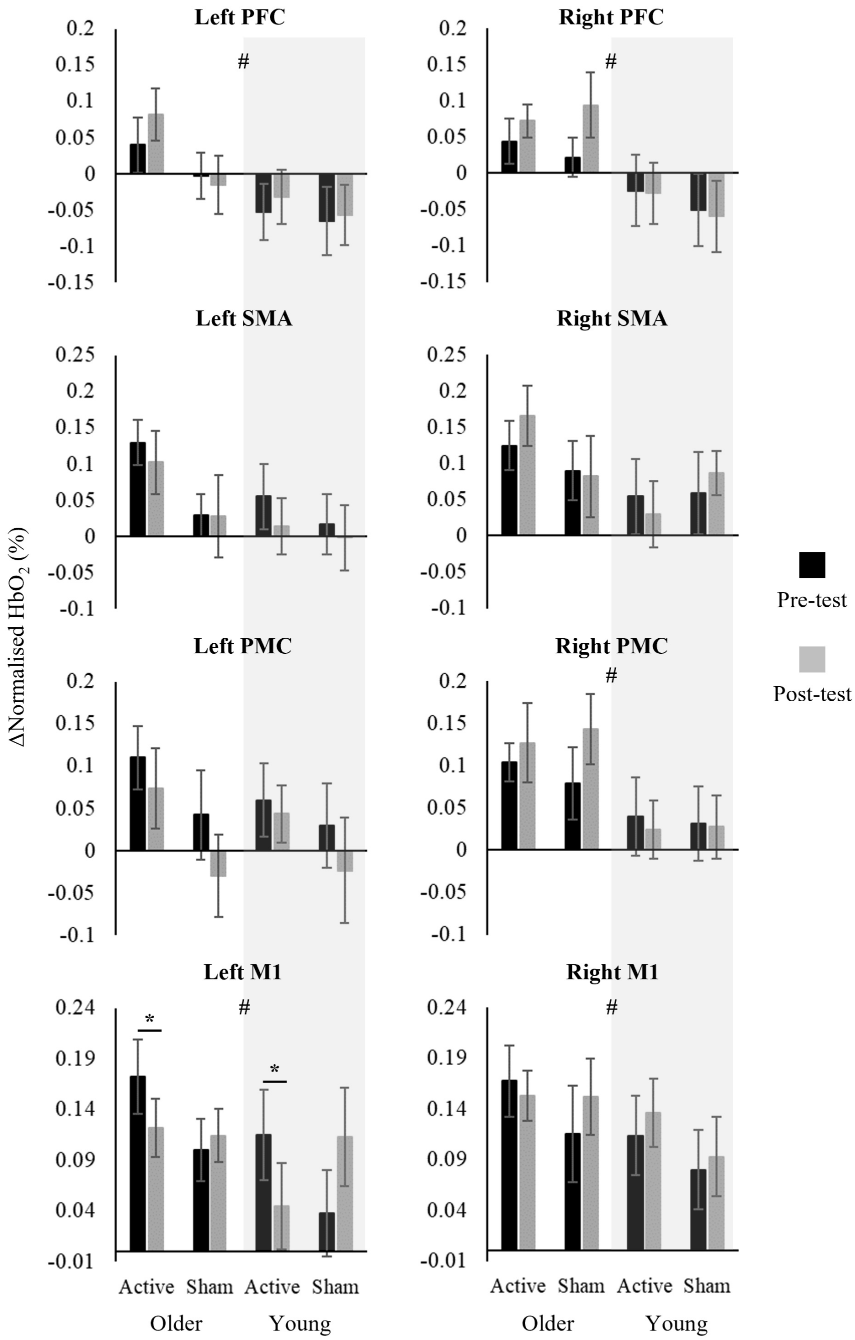

FIGURE 4 | Means and standard errors of change in oxygenated hemoglobin (ΔHbO_2 = DTW periods minus STW periods) in pre- and post-intervention walking test of active-Older adults (*n* = 10), sham-Older adults (*n* = 8), active-Young adults (*n* = 12) and sham-Young adults (*n* = 11). # indicates significant main effect of age group and * indicates significant interaction between stimulation condition and time.

$p < 0.001$, $\eta^2_p = 0.297$]. OA had higher body mass compared to YA (77.0 ± 4.4 kg; 64.3 ± 4.2 kg); OA walked at a slower treadmill speed than YA (2.71 ± 0.17 ms^{-2}; 3.87 ± 0.15 ms^{-2}), OA showed lower scores (fewer adverse effects) on the Adverse Effects of tDCS Questionnaire than YA (10.58 ± 0.55; 13.56 ± 0.50). There was no significant effect of stimulation condition.

The linear mixed effects models showed a main effect of intervention duration (0, 10, and 20 min) for the Borg scale [$F_{(2,108)} = 10.398$, $p < 0.001$, $\eta^2_p = 0.161$] (**Figure 3**). The perceived exertion increased throughout the tDCS + STW intervention with the Borg scale score being higher in the 10th min compared to 0 min ($p = 0.015$, $d = 0.728$) and in the 20th min compared to 0 min ($p < 0.001$, $d = 1.007$) and 10th min ($p = 0.039$, $d = 0.409$).

Linear mixed effects models did not show main effects of age group, stimulation condition, and time, in addition to interaction effects for the performance (% of error) in the cognitive digit vigilance task during DTW (**Table 2**).

Data from some participants were excluded from analysis because of excessive fNIRS noise across all channels (one from sham-OA group), or because of problems with the accelerometer recordings (one from sham-OA group and one from sham-YA group). Hence, fNIRS analysis was based on $n = 10$ for the active-OA, $n = 8$ for the sham-OA, $n = 12$ for the active-YA, and $n = 11$ for the sham-YA. The accelerometer analysis was based on $n = 10$ for the active-OA, $n = 8$ for the sham-OA, $n = 12$ for the active-YA, and $n = 10$ for the sham-YA.

Effect of Transcranial Direct Current Stimulation Combined With Treadmill Walking on ΔHbO_2 Levels

The linear mixed effects models showed a main effect of age group, with OA presenting higher ΔHbO_2 in the left PFC [$F_{(1,74)} = 5.348$, $p = 0.024$, $\eta^2_p = 0.067$], right PFC [$F_{(1,74)} = 11.859$, $p = 0.001$, $\eta^2_p = 0.138$], right PMC [$F_{(1,74)} = 6.601$, $p = 0.012$, $\eta^2_p = 0.082$], left M1 [$F_{(1,74)} = 4.579$, $p = 0.036$, $\eta^2_p = 0.058$], and right M1 [$F_{(1,74)} = 4.084$, $p = 0.047$, $\eta^2_p = 0.052$] compared to YA (**Figure 4**). In addition, an interaction effect between stimulation condition and time was found for ΔHbO_2 in the left M1 [$F_{(1,74)} = 4.795$, $p = 0.032$, $\eta^2_p = 0.061$] (**Figure 4**). *Post hoc* test showed that both OA and YA receiving active tDCS decreased left M1 ΔHbO_2 after the tDCS + STW intervention compared to pre-intervention ($p = 0.040$, $d = 0.615$). No other main effects of age group, stimulation condition or time, or interaction effects, were found.

Effect of Age, Time, and Intervention on Dual-Task-Related Gait Changes

Gait parameters are presented in **Table 2** and the summary of effects are presented in **Table 3**. A main effect of age group was observed for Δstride time variability [$F_{(1,72)} = 6.011$, $p = 0.017$, $\eta^2_p = 0.077$] and Δstride length variability [$F_{(1,72)} = 14.572$, $p < 0.001$, $\eta^2_p = 0.168$], with OAs presenting higher Δ values than YAs. There was a main effect of time for Δstride time variability [$F_{(1,72)} = 4.985$, $p = 0.029$, $\eta^2_p = 0.065$], showing that the difference in stride time variability between DTW and STW (delta value) decreased in participants post-intervention compared to pre-intervention. An interaction between age group and time was found for Δstance time ratio [$F_{(1,72)} = 4.798$, $p = 0.032$, $\eta^2_p = 0.062$] and Δstride time variability [$F_{(1,72)} = 5.928$, $p = 0.017$, $\eta^2_p = 0.076$]. *Post hoc* tests showed higher Δstride time variability in pre-intervention for OA compared to YA ($p = 0.001$, $d = 0.855$). In addition, OA increased Δstance time ratio ($p = 0.013$, $d = 0.645$) and decreased Δstride time variability ($p = 0.002$, $d = 1.001$) in post-intervention compared to pre-intervention, while no change was observed for YA. No other main effects of age, stimulation condition or time, or interaction effects, were found.

Association Between Change in Cortical Activity and Gait Parameters in Response to Intervention ($\Delta_{POST-PRE}$)

A negative correlation was observed between ΔHbO_2 in the left PFC and Δstride length variability for active groups (**Figure 5**). There were no other significant associations between ΔHbO_2 and changes in gait parameters that occurred in any of the groups.

DISCUSSION

In this study we investigated the effects of combined anodal tDCS applied over M1 and PFC, and treadmill walking on cortical activity and gait parameters in YA and OA. Contrary to our hypothesis, we found that active anodal tDCS + STW decreased M1 activity in both YA and OA and did not modify gait parameters. A negative correlation was observed between changes in PFC activity and stride length variability.

A novelty of this study was to apply tDCS over two brain areas, M1 and PFC as previous studies have applied the stimulation to these areas separately. These regions were selected as DTW involves both motor and higher executive function control (Petersen et al., 2001, 2012; Koenraadt et al., 2014). Our main findings showed that M1 ΔHbO_2 decreased following the active tDCS + STW intervention with no change in PFC. Previous studies have indicated that anodal tDCS increases excitability in the target area, due to postulated increased action potential firing rates, prolonged changes in membrane potential and decreased inhibitory interneural activity (Nitsche and Paulus, 2000; Nitsche et al., 2008; Murray et al., 2015; Hurley and Machado, 2018). Therefore, we expected to observe an increase in PFC and M1 activity. A possible explanation, according to the neural efficiency hypothesis, is that anodal tDCS may have improved the efficiency of M1 activity (Zarahn et al., 2007). Increased cortical activity has been considered a compensatory strategy for maintaining motor performance (Herold et al., 2017; Stuart et al., 2018). However, reduced cortical activity without changing motor performance demonstrates an improvement in neural efficiency, that is, individuals with higher neural ability display a lower energy consumption of the brain (Zarahn et al., 2007). Indeed, both YA and OA did not change the locomotor pattern post-intervention. Taken together, our findings showed that anodal tDCS over M1 contributes to improving neural efficiency to control walking when performing a cognitive task simultaneously.

A further possible explanation for decreased M1 activity after active tDCS + STW intervention is homeostatic metaplasticity. Bienenstock et al. (1982) developed a mathematical model, the Bienenstock–Cooper–Munro (BCM) theory, to describe modulation of synaptic excitability based on homeostatic metaplasticity of synapses. Homeostatic metaplasticity is a mechanism that maintains neuronal excitability within a physiological dynamic range (Murakami et al., 2012). This theory postulates that plasticity at a synapse is bidirectional, resulting in either long-term potentiation (LTP) or long-term depression (LTD), and that the threshold for induction of LTP versus LTD of synapses is not stable but dynamic

TABLE 3 | Summary of main effect and interactions in 3-way linear mixed models analyses of gait parameters.

Gait parameters	Main effect			Interactions	
	Age group[c]	Intervention group[d]	Time[e]	Age × Time	Intervention × Time
Cadence	ns	ns	ns	ns	ns
Stance time ratio[a]	ns	ns	ns	OA: Pre < Post	ns
Stride time variability	ns	ns	Pre > Post	Pre: OA > YA OA: Pre > Post	ns
Stride length variability	ns	ns	ns	ns	ns
Cognitive task errors[b]	ns	ns	ns	ns	ns

[a]Ratio between the foot contact time and the stride time. [b]Digit vigilance task. [c]Older adults (OA) vs. young adults (YA). [d]Active tDCS + STW vs. Sham tDCS + STW. [e]Pre- vs. post-intervention. ns: not significant.

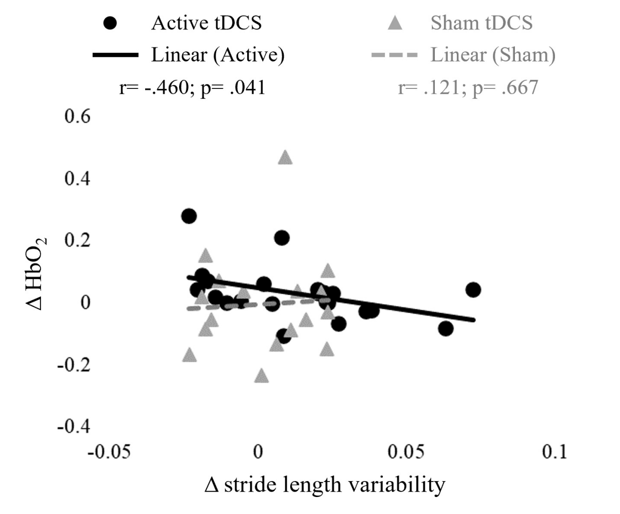

FIGURE 5 | Correlations between changes in oxygenated hemoglobin (ΔHbO_2) in the left prefrontal cortex (PFC) activity and stride length variability in responses to active and sham tDCS stimulation ($\Delta_{POST-PRE}$).

(Bienenstock et al., 1982; Murakami et al., 2012). The BCM model states that prior excitation will elevate the excitation threshold and thus decrease the predisposition for excitation, whereas prior inhibition will lower the excitation threshold and thus increase the predisposition for excitation (Murakami et al., 2012; Hurley and Machado, 2017). Therefore, as both tDCS and treadmill walking increase cortical excitability, performing DTW after tDCS + STW may facilitate LTD (decreased M1 activity).

We did not observe statistical differences in PFC ΔHbO_2, gait parameters or in the cognitive task following active tDCS + STW intervention. There are several possible explanations. Firstly, we have used a small electrode size (3 cm × 3 cm). A small electrode allows stimulating a more focal area while a large anodal electrode targets a more widespread region (Bikson et al., 2013; Thair et al., 2017). Stimulating not only the area underlying the anodal electrode, but also surrounding areas within the regions may enhance the tDCS benefits. For example, Chen and Machado (2017) using a 3 cm × 3 cm anodal electrode did not show benefits on saccadic eye movement behavior, but Chen et al. (2018) showed improvements in oculomotor control following tDCS using 5 cm × 7 cm anodal electrode. Secondly, the stimulation intensity may have been too low. We applied 0.6 mA, whereas most studies have used either 1.0 or 2.0 mA (de Paz et al., 2019; Beretta et al., 2020). We selected this intensity to ensure the current density was within the recommended safety limit of 0.029–0.08 mA/cm^2 (Nitsche et al., 2008). The surface area of our anodal electrodes was 9 cm^2 resulting in a current density of 0.067 mA/cm^2. Several studies that used 1–2 mA also reported inconclusive results (de Paz et al., 2019; Beretta et al., 2020). While some studies have shown positive effects of stimulation combined with training in gait parameters (Kaski et al., 2014b,a; Park et al., 2015; Manenti et al., 2016; Ishikuro et al., 2018), others have not (Costa-Ribeiro et al., 2016, 2017; Kumru et al., 2016; Manenti et al., 2016; Fernández-Lago et al., 2017; Seo et al., 2017; Yotnuengnit et al., 2018). Although OA decreased stride time variability in the post-compared to pre-intervention, this was not related to active tDCS + STW, since both sham and active interventions presented a reduction. This indicates a training effect for OA, who are generally less familiar with treadmill walking than YA. Thirdly, studies that observed positive effects of anodal tDCS combined with training have investigated patients with neurological disorders, such as Parkinson's disease and stroke (de Paz et al., 2019; Beretta et al., 2020). Fourthly, the lack of change in gait parameters following active tDCS + STW may be explained by the physically active participants who all performed more than 150 min of physical activity per week. A single session of 20 min treadmill walking combined with low current tDCS may therefore not be sufficient to induce gait changes (Silva et al., 2019). Specifically, regarding the cognitive task, a possible reason for no observed improvement could be the high cognitive functionality of the OA group (no difference in MoCA between age groups) and the floor effect (participants presented a low percentage of errors in the cognitive digit vigilance task – **Table 2**), reducing the amount participants could improve. We recommend the cognitive task is standardized by age group in future studies (de Rond et al., 2021). Taken together, further investigation is necessary to optimize tDCS protocols in gait rehabilitation.

Although the tDCS + STW intervention was not found to increase PFC HbO_2, within the active tDCS groups, partial correlation showed that higher increases in PFC activity were associated with greater decreases in stride length variability. Our data also showed that OA presented higher activity bilaterally in the PFC and M1, and unilaterally in the right PMC compared to YA, which may reflect a mechanism to compensate for age-related decrease in gait automaticity (Stuart et al., 2018; Al-Yahya et al., 2019). In addition, OA presented higher gait variability than YA, which suggests reduced movement automaticity (Hausdorff et al., 2001; Verghese et al., 2009; Sawa et al., 2014; Aboutorabi et al., 2016). Taken together, these findings may indicate that the combined intervention could expand the availability of prefrontal executive-attentional resources to be allocated to the control of walking, leading to better movement automaticity (da Conceição et al., 2021).

A key strength of this study is the sham protocol, which was effective in blinding participants to the tDCS condition. Indeed, we did not observe a difference in the adverse events questionnaire between the sham and active groups, which confirms the participant blinding. Also, the concurrent assessment of multiple cortical areas (PFC, PMC, SMA, and M1) while walking together with gait parameters provides better understanding of aspects involved in the gait control and the potential mechanisms underlying gait improvements obtained with the combined intervention. However, this study presents some limitations. The small sample size is an important limitation resulting in low statistical power and may account for the lack of significant change in fNIRS signals, gait parameters and cognitive tasks following anodal tDCS. The small sample size may also have prevented us from finding other associations between changes in cortical activity and gait parameters. The absence of a control group who did not perform any of the intervention protocols or an isolated tDCS session limits our interpretations. The study only involved a single session rather than a series of sessions which may have provided significant longitudinal results (El-Sayes et al., 2019). The number of women and men in the groups was unbalanced. Previous studies have reported sex-specific cortical activation, which suggests that sex may affect fNIRS signals (Leon-Carrion et al., 2006; Li et al., 2010; Baker et al., 2016). Another limitation concerns the treadmill task. Previous studies have reported a significant difference in hemodynamic data when individuals walked on a treadmill compared to overground (Clark et al., 2014; Thumm et al., 2018) due to a treadmill acting as an external regulator of gait (Suzuki et al., 2004; Harada et al., 2009). There are limitations in recording fNIRS signals as we did not use short-separation channels to control for scalp blood flow. However, we applied Wavelet-MDL detrending to remove unknown global trends from our data, which has been shown to be acceptable (Jang et al., 2009; Herold et al., 2017; Vitorio et al., 2017). Another limitation is the use of a subjective scale (Borg) to assess exercise intensity. Although the Borg scale is a valid tool for monitoring exercise intensity (Scherr et al., 2013), an objective physiological measure (e.g., heart rate) would be more precise in order to ensure that all four groups experienced the similar intensity of walking (Chen et al., 2002). A further limitation is that the older adults who frequently volunteer for studies are often physically more active and cognitively higher functioning than is typical for their age group, which may have lessened the chances of the older adults benefiting from the active combined intervention due to less room for improvement relative to the general population. Therefore, we recommend addressing these limitations in future studies.

In conclusion, an intervention using anodal tDCS applied to both PFC and M1 cortical regions combined with STW decreased M1 cortical activity during DTW in both YA and OA. As gait parameters remained unchanged, this suggests an improvement in neural efficiency. In addition, higher increases in PFC activity after combined tDCS + STW intervention is related to better gait automaticity.

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 Newcastle University Faculty of Medical Sciences Ethics Committee (Ref. 6770/2018). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DO-S designed the study, collected, analyzed, and interpreted the data, and drafted the manuscript for intellectual content. AP designed and conceptualized the study, interpreted the data, and revised the manuscript for intellectual content. AI designed the study, collected, analyzed, and interpreted the data, and revised the manuscript for intellectual content. LTBG and LR interpreted the data and revised the manuscript for intellectual content. MB designed the study, interpreted the data, and revised the manuscript for intellectual content. All authors approved the final manuscript.

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Latin Dance and Working Memory: The Mediating Effects of Physical Activity Among Middle-Aged and Older Latinos

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Background: Physical activity (PA) is a promising method to improve cognition among middle-aged and older adults. Latinos are at high risk for cognitive decline and engaging in low levels of PA. Culturally relevant PA interventions for middle-aged and older Latinos are critically needed to reduce risk of cognitive decline. We examined changes in cognitive performance among middle-aged and older Latinos participating in the BAILAMOS^{TM} dance program or a health education group and compared the mediating effects of PA between group assignment and change in cognitive domains.

Methods: Our 8-month randomized controlled trial tested BAILAMOS^{TM}, a 4-month Latin dance program followed by a 4-month maintenance phase. A total of 333 older Latinos aged 55+ were randomized to either BAILAMOS^{TM}, or to a health education control group. Neuropsychological tests were administered, scores were converted to z-scores, and specific domains (i.e., executive function, episodic memory, and working memory) were derived. Self-reported PA was assessed, and we reported categories of total PA, total leisure PA, and moderate-to-vigorous PA as minutes/week. A series of ANCOVAs tested changes in cognitive domains at 4 and 8 months. A mediation analysis tested the mediating effects of each PA category between group assignment and a significant change in cognition score.

Results: The ANCOVAs found significant improvement in working memory scores among participants in the dance group at month 8 [$F_{(1,328)} = 5.79$, $p = 0.017$, $d = 0.20$], but not in executive functioning [$F_{(2,328)} = 0.229$, $p = 0.80$, Cohen's $d = 0.07$] or episodic memory [$F_{(2,328)} = 0.241$, $p = 0.78$, Cohen's $d = 0.05$]. Follow-up mediation models found that total PA mediated the relationship between group assignment and working memory, in favor of the dance group (β = 0.027, 95% CI [0.0000, 0.0705]). Similarly, total leisure PA was found to mediate this relationship [β = 0.035, 95% CI (0.0041, 0.0807)].

Conclusion: A 4-month Latin dance program followed by a 4-month maintenance phase improved working memory among middle-aged and older Latinos. Improvements in working memory were mediated by participation in leisure PA. Our results support the current literature that leisure time PA influences cognition and highlight the importance of culturally relevant PA modalities for Latinos.

Clinical Trial Registration: [www.ClinicalTrials.gov], identifier [NCT01988233].

Keywords: cognition, exercise, disparities, dance, physical activity

INTRODUCTION

Twelve percent of older Latinos in the U.S. are currently diagnosed with Alzheimer's Disease (AD), and it is estimated that the number of Latinos with AD will increase by 832% by 2060 (Wu et al., 2016). Currently, there is no cure for AD; however, evidence suggests that protective factors for AD include regular physical activity (PA) (Blondell et al., 2014), cognitively and mentally stimulating leisure activities (Wilson et al., 2012), social engagement, and having a rich social network (Marioni et al., 2015). Latin dance is a particularly promising PA modality that targets these factors and is a culturally acceptable type of PA for middle-aged and older Latinos (Valenzuela et al., 2013; Marquez et al., 2014a).

Latin dance has long been part of the history, socialization, and culture of Latinos (Gonzalez et al., 1998). Dance as a PA modality for Latinos may evoke positive emotional responses that encourage PA participation in a population with low levels of PA (Arredondo et al., 2015). Latinos have cited dance as an important and desirable component to community-based programs (Larsen et al., 2015; Predovan et al., 2019). Furthermore, engaging in dance has been shown to improve or maintain cognition (Hamacher et al., 2015; Hwang and Braun, 2015; Merom et al., 2016; Predovan et al., 2019; Muiños and Ballesteros, 2021), partly due to the learning component and coordination of dancing (Voelcker-Rehage and Niemann, 2013; Rehfeld et al., 2017), the multisensory demands of the activity (Thøgersen-Ntoumani et al., 2018), the timing, synchronization and sequences of moves, and the energy expenditure associated with movement (Keogh et al., 2009). Randomized controlled trials (RCTs) have examined changes in cognitive performance among several types of dance styles including, ballroom dancing (Lazarou et al., 2017), Cha-Cha (Kim et al., 2011), and a blend of styles (e.g., line dance, jazz dance, rock'n roll, Latin, and square dance) (Hamacher et al., 2015) and have demonstrated changes in global cognition, executive function, episodic and working memory, and attention. Despite the benefits and appeal of dance, PA programs and interventions rarely implement dance programs *specifically* for Latinos, a historically excluded population at high risk of chronic disease, mobility disability (Angel et al., 2015), and cognitive impairment (Wu et al., 2016).

Given the need to address health inequities in Latinos, Marquez and colleagues created a Spanish-language, Latin dance program (BAILAMOS^{TM}—Balance and Activity In Latinos, Addressing Mobility in Older Adults) (Marquez et al., 2014a) for middle-aged and older Latinos to increase PA, thereby reducing risk of chronic diseases, mobility disability, and cognitive impairment. An initial pilot study with twelve participants demonstrated that self-reported PA increased significantly and small positive effects for executive function and speed of processing were seen in participants, all of whom received the Latin dance program (Marquez et al., 2014a). Following that small pilot, a two-group pilot trial was conducted to examine differences in cognitive performance among 57 older Latinos randomized to either the BAILAMOS^{TM} dance program or a health education program (Marquez et al., 2017). Findings showed greater improvement in episodic memory in the dance group compared to the health education group. Balbim et al. (2021) examined the impact of the BAILAMOS^{TM} dance program on physical activity, brain functional connectivity, and cognitive performance among 10 participants who received the program. Participation in the program led to an increase in self-reported moderate leisure-time PA, increases in brain functional connectivity, but no statistically significant changes in cognitive performance. These studies demonstrated promising findings for increasing PA, cognition, and brain function; however, these studies were limited by small sample sizes and short follow-up periods, making advanced analytical methods difficult to conduct. Therefore, the purpose of the present study was to examine the secondary outcome of changes in cognitive performance in a large sample of middle-aged and older Latinos participating in the BAILAMOS^{TM} dance program or a health education control group at 4-months and 8-months post-intervention and compare the mediating effects of types of PA (i.e., minutes/week of total PA, minutes/week of total leisure PA, and minutes/week of moderate-to-vigorous PA), and between group assignment and change in cognitive domains.

MATERIALS AND METHODS

Participants and Design

Study details regarding recruitment, intervention content, program delivery, and flow of participants have been previously described (Marquez et al., 2014b). Briefly, participants ($N = 333$) were low-active, at risk for disability, and cognitively healthy middle-aged and older Latinos residing in Chicago and recruited from study sites, churches with Spanish masses, health centers, presence at supermarkets, and senior fairs, to name a few. Participants were randomized into one of two conditions: (1) the 4-month, twice-weekly (1 h per session) BAILAMOS^{TM} Latin dance program consisting of four dance styles (e.g., merengue, bachata, cha cha cha, and salsa), followed by a 4-month maintenance phase or (2) a 4-month, once weekly (2 h per session) health education condition that included curriculum on stress, My (food) Pyramid, food labels, diabetes, cancer, osteoporosis, immunizations, building a better memory, and making the most of medical appointments. The BAILAMOS^{TM} Latin dance program encourages PA participation outside of the program to increase PA in participants' daily lives, as the dance instructor consistently mentioned engaging in PA outside of dancing. The 4-month maintenance phase used a train the trainer model wherein indigenous leaders, participants who were sociable, proficient at dancing, and regularly attended the program were trained by the dance instructor to become dance instructors and teach the BAILAMOS^{TM} dance program. During the 4-month maintenance phase, the indigenous leaders took attendance, led the dance classes for the participants, and continued the same structure of the initial 4-month program at different facilities. Participants in both conditions received all sessions and materials in Spanish. Assessments were conducted at baseline, the primary (month 4) and secondary (month 8) timepoints.

Measures

Demographics

Information about age, gender, body mass index, education, and marital status was obtained.

Neuropsychological Tests

We utilized a set of neuropsychological tests (Wilson et al., 2002) which have been adapted to Spanish (Krueger et al., 2009). Seven neuropsychological tests that assess three domains (i.e., executive function, working memory, and episodic memory) that have been found to decrease with age but also to be influenced by regular PA (Kramer et al., 2006) were administered at baseline, the primary (month 4) and secondary (month 8) timepoints. Individual tests were combined to form composite scores for executive function, working memory, and episodic memory by averaging the z scores converted from each test (Wilson et al., 2002). Those z scores were computed by using the population mean and SD from the baseline measurements. Each test is described below.

Executive Function

Trail Making Test (TMT)-Parts A and B (Army Individual Test Battery, 1944) consist of two parts. The test requires a participant to draw lines sequentially connecting 25 encircled numbers randomly distributed on a page (Part A) and encircled numbers and letters in alternating order (Part B). The score is the time required to complete each task. Lower values reflect better performance; therefore z-scores were multiplied by −1.

Stroop Neuropsychological Screening Test: We used a short form (Wilson et al., 2005) of the Stroop Neuropsychological Screening Test (Trenerry et al., 1989) in which the participant is shown a list of color names in different ink colors, and first asked to read the words (as opposed to the color of the font), and then asked to name the color of the font (as opposed to the word itself). The scores are the number of words named correctly in 30 s minus the number of errors; and the number of colors named correctly in 30 s minus the number of errors.

Word fluency (Welsh et al., 1994) asks participants to generate as many examples as possible from two semantic categories (animals; fruits and vegetables) in separate 60-s trials. The word fluency score is the sum of the number of animals generated with the number of fruits and vegetables generated.

Symbol Digit Modalities Test (Smith, 1982) involves identifying and naming the digits which belong with consecutively presented symbols. The score is the number of digits correctly paired with symbols in 90 s.

Working Memory

Digit Span Test (Wechsler, 1987) has two parts. Digit strings of increasing length are read, and the participant is asked to repeat each string forward (Digit Span Forward) or backward (Digit Span Backward). The score is the number of correctly retrieved strings in each part.

Digit Ordering (Cooper et al., 1991; Wilson et al., 2005) involves reading digit strings of increasing length and the participant is asked to reorder the digits and say them in ascending order. The score is the number of correctly reordered strings.

Episodic Memory

Logical Memory I and II (Wechsler, 1987) has two parts. A brief story is read to the participant who is then asked to retell it immediately (I) and after a 5-min delay filled with other activities (II). The score is the number of the 25 story units recalled immediately (I) and after the delay (II).

Physical Activity

Self-reported PA was assessed *via* the Community Healthy Activities Model Program For Seniors (CHAMPS) Physical Activity Questionnaire for Older Adults (Stewart et al., 2001). This is a change-sensitive PA scale that assesses weekly frequency and duration of lifestyle PA (broken down into leisure time, household, occupational, transportation, and total PA) typically undertaken by older adults, reported as minutes per week. The CHAMPS has been translated into Spanish and used with older Latino adults (Rosario et al., 2008). We report categories of *total PA* (minutes of light and moderate and vigorous PA), *total leisure PA* (minutes of light and moderate and vigorous leisure PA), and *moderate-to-vigorous PA* (MVPA) as minutes/week.

Statistical Methods

Sample size analysis, report on missing data values, and multiple imputation approaches have been previously reported (Marquez et al., 2022). The primary objective was investigated using a series of ANCOVAs to assess whether group assignment predicted change in each of the three cognitive domains (e.g., executive function, working memory, and episodic memory) at months 4 and 8. Statistically significant ($p < 0.05$) findings found at the multivariate level were followed by reporting results from the univariate tests. Changes in the primary (month 4) and secondary (month 8) time points were tested controlling for baseline cognitive values, which were treated as a covariate, with follow-up values set as the dependent variables. Age was the only demographic variable that was controlled when testing the hypotheses.

The secondary objective further investigated which PA category explained any significant between-group changes in cognitive domains at months 4 and 8 by conducting mediation analyses. Mediation models were assessed using the PROCESS macro for SPSS. Prior to analysis, all variables were standardized to z-score change values between baseline and follow-up measures based on recommended guidelines (Hayes et al., 2017). The mediation models tested if PA mediated the relationship between group assignment (dance intervention vs. control) and a significantly changed cognition score. This model was performed three times to test mediating effects for each PA category (total minutes of PA, total leisure PA, and MVPA). Statistical significance was calculated using 95% bias-corrected confidence intervals on the basis of 5,000 bootstrap samples. The effects are considered significant when the confidence intervals do not cross through zero (Preacher and Hayes, 2008; Hayes et al., 2017; Schoemann et al., 2017).

RESULTS

Participants were on average 64.9 (SD = 7.09) years of age with an average BMI of 31.14 (SD = 4.78). The majority of participants were female (84.4%), with 8.38 (SD = 4.01) years of education, and 48.9% were married. Age was statistically different (0.050) as the significance level was defined as <0.05 and was controlled when conducting hypotheses tests on any baseline or demographic variables including baseline total PA, total leisure PA, and moderate-to-vigorous PA. For cognitive performance scores, there were significant between-group differences for Trail Making Test A and Stroop CW (**Table 1**).

A series of repeated measures ANCOVA were performed to test between group differences for each cognitive domain with age as a covariate (**Table 2**). There was a significant group difference in working memory between the two groups [Wilk's $\lambda = 0.98$, $F_{(2,328)} = 3.13$, $p = 0.045$]. Follow-up univariate tests found no significant between-group differences at month 4 [$F_{(1,328)} = 0.392$, $p = 0.532$, $d = 0.13$], but the experimental dance group demonstrated a significant improvement in working memory at month 8 of the study [$F_{(1,328)} = 5.79$, $p = 0.017$, $d = 0.20$]. Multivariate analyses that tested change in executive functioning [Wilk's $\lambda = 0.99$, $F_{(2,328)} = 0.229$, $p = 0.80$] and episodic memory [Wilk's $\lambda = 0.99$, $F_{(2,328)} = 0.241$, $p = 0.78$] were not significant between the two groups at 4 and 8 months.

Mediation Analysis

The significant findings of working memory at month 8 were further investigated with mediation tests (**Figure 1**). The first mediation model found that group assignment (Path A) predicted total PA time ($\beta = 0.23$, 95% CI [0.0174, 0.4463], $p = 0.034$) in favor of the dance group. Total PA time in turn (Path B), predicted higher working memory scores ($\beta = 0.12$, 95% CI [0.0098, 0.2247], $p = 0.032$). Indirect path analysis revealed total PA time mediated the relationship between group assignment and working memory ($\beta = 0.027$, 95% CI [0.0000, 0.0705]) and the direct pathway (Path C') crossed through zero ($\beta = 0.10$, 95% CI [−0.1134, 0.3152]), thus satisfying the requirements for complete mediation.

The second mediation model found group assignment predicted total leisure PA (Path A) ($\beta = 0.25$, 95% CI [0.0397, 0.4593], $p = 0.025$), and total leisure PA predicted working memory (Path B) ($\beta = 0.14$, 95% CI [0.0367, 0.2510], $p = 0.009$) in favor of the dance group. The indirect path (Path AB) mediated the relationship between group assignment and working memory ($\beta = 0.035$, 95% CI [0.0041, 0.0807]), while the direct pathway from group assignment to working memory revealed the 95% CI to cross through zero ($\beta = 0.11$, 95% CI [−0.1048, 0.3227]), also supporting a mediating effect.

Finally, for the third mediation model, group assignment predicted MVPA (Path A) ($\beta = 0.42$, 95% CI [0.1248, 0.7088], $p = 0.054$); however, MVPA did not predict working memory (Path B) ($\beta = 0.02$, 95% CI [−0.1244, 0.1585], $p = 0.812$). Confidence intervals of the direct pathway (Path C') ($\beta = 0.31$, 95% CI [−0.0203, 0.6035]) did not cross through zero, and indirect effects (Path AB) crossed through zero ($\beta = 0.01$, 95% CI [−0.0392, 0.0679]), denoting non- mediated effect.

DISCUSSION

The present study examined whether participation in the BAILAMOS^{TM} dance program improved cognitive performance compared to a health education control group and investigated which PA category predicted cognitive changes among middle-aged and older Latinos over eight months. The study showed that participants who were randomized to the 4-month Latin dance program followed by a 4-month maintenance phase improved in working memory compared to participants in the health education control group. Findings indicate that improvements in working memory were mediated by participation in total PA and total leisure PA at 8 months only. While effect sizes (Cohen's *d*) were modest in this study, small effect sizes are typically found in RCTs in older adults (Erickson et al., 2019). These findings support the current literature on the influence of leisure PA and total PA on cognitive performance and highlight the importance of culturally appropriate PA modalities for middle-aged and older Latinos.

The between-groups analysis between the two groups at 4-months found no differences in any of the cognitive measures, which is similar to findings from a small pilot examining the BAILAMOS^{TM} dance program in older Latinos (Balbim et al., 2021). However, our study found improved working memory at month 8 in the dance group. This finding is in line with the literature demonstrating that longer dance interventions (>4 months) are needed to detect changes in cognitive performance. For example, Fausto and colleagues found that African American older adults who received a 5-month cardio-dance program consisting of dance routines and steps from hip-hop, merengue, samba, cumbia, and salsa improved attention compared to a propensity-matched control group (Fausto et al., 2021). Another study by Lazarou et al. (2017) reported that participants in a 10-month international ballroom

TABLE 1 | Demographic characteristics of the sample.

Baseline characteristics	Control condition (*N* = 166)	Experimental condition (*N* = 167)	*p*
	Mean (SD)	Mean (SD)	
Age	65.67 (7.68)	64.14 (6.39)	0.05
Female	141	140	0.78
BMI	30.84 (5.05)	31.47 (4.54)	0.19
Years of education	8.40 (4.10)	8.35 (3.91)	0.91
Marriage/Common Law	65	98	0.92
CHAMPS			
Total PA	695.06 (438.54)	717.16 (533.340)	0.68
Total Leisure-time PA	341.75 (334.56)	339.79 (411.49)	0.96
Moderate-to-vigorous PA	148.73 (229.87)	169.21 (322.92)	0.51
Cognitive tests			
TMT-A	54.4 (27.25)	48.41 (22.88)	0.03
TMT-B	191.11 (86.94)	177.22 (85.40)	0.15
Stroop-C	51.56 (13.85)	53.93 (14.65)	0.13
Stroop-CW	17.76 (6.79)	20.13 (8.59)	0.01
Word fluency	33.87 (8.38)	34.46 (8.24)	0.52
SDMT	30.83 (13.25)	32.32 (12.12)	0.29
Digit span forward	5.03 (1.70)	4.91 (1.76)	0.55
Digit span backward	3.76 (1.71)	3.74 (1.64)	0.92
Digit ordering	5.27 (1.95)	5.55 (1.89)	0.20
Logical memory-immediate	9.18 (3.76)	9.37 (3.63)	0.64
Logical memory-delayed	7.80 (3.63)	7.80 (3.69)	0.99

Abbreviations: CHAMPS, Community Healthy Activities Model Program For Seniors; TMT, Trail Making Test; SDMT, Symbol Digit Modalities Test.

TABLE 2 | Means and standard deviations of cognitive domain scores by study condition, with effect sizes for within and between condition differences.

Constructs	Condition E (*N* = 167) C (*N* = 166)	Baseline *z-score*	Month 4 *z-score*	Month 8 *z-score*	Cohen's *d* within condition (Month 4)	Cohen's *d* within condition (Month 8)	Cohen's *d* between condition (Month 4)	Cohen's *d* between condition (Month 8)
Cognitive Domain								
Working memory	E	0.013	0.153	0.118	0.17	0.24	0.16	0.20
Working memory	C	0.016	−0.120	−0.090	0.02	0.04		
Episodic memory	E	0.015	0.061	0.055	0.27	0.44	−0.03	0.05
Episodic memory	C	0.012	−0.083	−0.098	0.30	0.39		
Executive functioning	E	−0.069	0.106	0.101	0.00	0.09	0.08	0.07
Executive functioning	C	0.072	−0.111	−0.110	−0.07	0.01		

dancing program improved in global cognition, reaction time, visuospatial skills, selective attention, and attentional switching. Our study found an improvement in working memory, and this finding is especially pertinent because working memory decline has been recognized as one of the primary contributing factors to cognitive impairment in older adults (Park et al., 2002). Therefore, Latin dance could be an important strategy to improve or maintain working memory among middle-aged and older Latinos, a population at high risk of cognitive decline.

Our findings demonstrated that changes in working memory at 8 months were mediated by total PA and total leisure PA. This finding suggests that PA categories may function as a mechanism to improve working memory. Studies have suggested that different types of PA may determine the extent to which PA impacts cognition (Quigley et al., 2020). For example, Quigley et al. (2020) concluded that single PA modes are effective in inducing improvements in cognition among older adults, but combined PA modes may offer magnified cognitive benefits. The advantage of dancing is that it is a PA mode that embeds aerobic PA and neuromotor PA (i.e., balance and proprioceptive training). Furthermore, participants in the Latin dance group were provided with a PA modality that facilitated an increase in their total PA and functioned as a leisure type of PA.

Changes in working memory at 8 months may have been due to several reasons. First, dancing poses a high demand on attention and memory for individuals. Participants initially learned four dance styles. During the 4-month maintenance phase, four additional dance moves were added to each dance

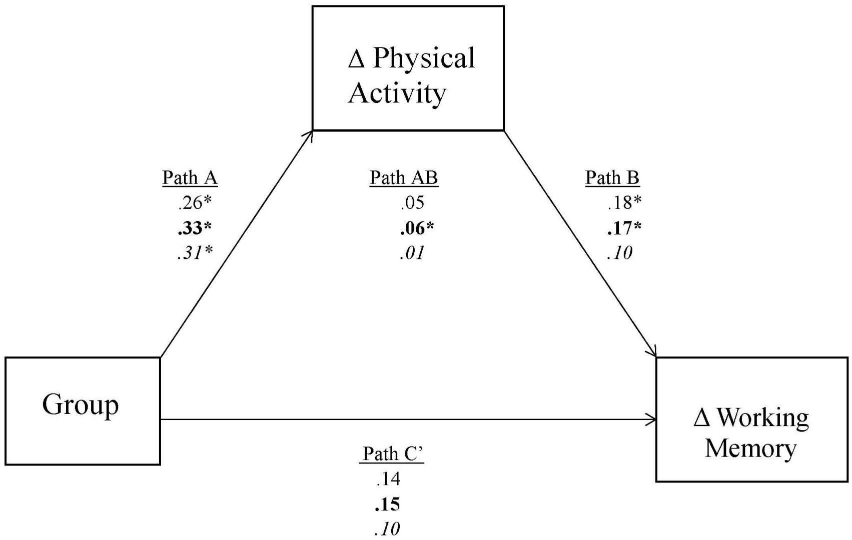

FIGURE 1 | Mediation model. Coefficients in standard font, bolded font, and italics represent total physical activity time, total leisure time physical activity, and moderate-to-vigorous physical activity, respectively. *Significance at $p < 0.05$. Group compares experimental vs. control condition.

style. Participants were able to practice what they learned during the maintenance phase, therefore the process of recalling steps and learning new dance steps may be due to the working memory process known as chunking information (Tulving and Craik, 2000). Participants in the dance intervention did this through the process of combining dance steps into sequences. For example, participants learned the side basic, back basic, and backside basic dance steps independently, which then were chunked into what is known to be the salsa dance style. Similar to the way the brain manipulates information into chunks, here we see the same process happening with the learning of different Latin dance styles, which helps to explain the improvement in working memory scores. Second, participants continued the dance program for an additional 4 months (maintenance phase). Indigenous leaders in the treatment group received training on how to continue the dance program without a professional instructor during the maintenance phase while the health education group stopped meeting. Therefore, with the train the trainer model, participants were provided the tools and training necessary to continue leading the program. Furthermore, dance participants may have felt empowered to implement strategies learned to overcome PA barriers, strengthened social ties, and continue engaging in a cognitively stimulating activity (e.g., dance). This study highlights the importance of implementing dance as a PA modality to increase PA, thereby, improving working memory and underscores how imperative it is to provide tools and training to create sustainable community programs led by community members.

Our study had several strengths including a large sample of community dwelling older, Spanish-speaking Latinos, a group that is rarely included in large RCTs, but has a high level of need for health-related interventions. The study also included a culturally relevant PA intervention (i.e., dance) with a 4-month maintenance phase embedded within the program. The study also had several limitations. First, PA was self-reported; thus, PA may be over- or under-estimated. Second, participants resided in Chicago and a majority identified as Mexican American, thereby limiting generalizability of findings to other geographic areas and other Latino subgroups. For the cognitive outcomes, improvements in cognitive performance should be interpreted with caution considering potential practice effects; however, the small changes observed in the control group suggest that practice effects, if any, are small. Also, no further follow-up was conducted to determine whether improvement in working memory were maintained. Lastly, the *a priori* sample size calculation of the trial was not performed specifically for the mediation analyses, but rather based on the primary outcome of changes in PA.

In sum, this study underscores the importance of creating and delivering culturally relevant, community-based Latin dance programs that promote total PA and function as a leisure time PA for Latinos. Furthermore, implementing maintenance phases to create more sustainable programs and empowering community members to lead programs is critical to create a culture of health. Future studies may consider including longer follow up periods to determine the duration of dance intervention effect on cognition.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

SA wrote the manuscript with feedback and guidance from NK, GB, and DM. NK conducted the statistical analysis. RW, JW, SH, DB, MB, EM, PV, IM, and TW provided critical feedback. All authors contributed to the final version of the manuscript.

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Multiple routes to help you roam: A comparison of training interventions to improve cognitive-motor dual-tasking in healthy older adults

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Cognitive-motor dual-tasking is a complex activity that predicts falls risk and cognitive impairment in older adults. Cognitive and physical training can both lead to improvements in dual-tasking; however, less is known about what mechanisms underlie these changes. To investigate this, 33 healthy older adults were randomized to one of three training arms: Executive function (EF; *n* =10), Aerobic Exercise (AE; *n* =10), Gross Motor Abilities (GMA; *n* =13) over 12 weeks (1h, 3×/week). Single and dual-task performance (gait speed, m/s; cognitive accuracy, %) was evaluated before and after training, using the 2-back as concurrent cognitive load. Training arms were designed to improve cognitive and motor functioning, through different mechanisms (i.e., executive functioning – EF, cardiorespiratory fitness – CRF, and energy cost of walking – ECW). Compared to baseline, we observed few changes in dual-task gait speed following training (small effect). However, dual-task cognitive accuracy improved significantly, becoming facilitated by walking (large effect). There were no differences in the magnitude of improvements across training arms. We also found that older adults with lower cognitive ability (i.e., MoCA score<26; *n* =14) improved more on the dual-task cognitive accuracy following training, compared to older adults with higher cognitive ability (i.e., MoCA ≥26; *n* =18). Taken together, the results suggest that regardless of the type of intervention, training appears to strengthen cognitive efficiency during dual-tasking, particularly for older adults with lower baseline cognitive status. These gains appear to occur via different mechanisms depending on the form of intervention. Implications of this research are paramount, as we demonstrate multiple routes for improving cognitive-motor dual-tasking in older adults, which may help reduce risk of cognitive impairment.

KEYWORDS

aging, executive function, gait, dual-task, exercise, cognitive training

Introduction

Cognitive-motor dual-task performance (e.g., walking while talking) in older adults has been shown to predict future physical and cognitive decline, including mild cognitive impairment and dementia (Montero-Odasso et al., 2012). Cognitive-motor dual-tasking is a multi-faceted behavior, involving cognitive processes, particularly executive functions (EFs), as well as motor skills. The complex interaction between cognitive and motor domains helps explain why different forms of cognitive or physical interventions have been found to maintain or improve dual-task performance in healthy older adults (Berryman et al., 2014; Wollesen and Voelcker-Rehage, 2014; Fraser et al., 2017). Nevertheless, the potential mechanisms which underlie improvements in dual-task performance across different training modalities are less well-understood. Therefore, the primary aim of this study was to compare the improvements of three different interventions on dual-task performance in healthy older adults and to investigate the mechanisms that could explain these improvements.

As individuals grow older, there is a greater reliance on cognitive resources, particularly EFs, when completing a motor task, such as walking (Hausdorff et al., 2005). This is well-supported by dual-task experiments, wherein dual-task costs (DTCs), or the decrement observed during dual-compared to single-task performance, are found to be greater in older adults compared to younger adults (Li et al., 2001). This decrement in performance has also been shown to occur in older adults at lower levels of cognitive load (eg., Srygley et al., 2009), and with increased physical task complexity (e.g., usual vs. fast paced walking; Krampe et al., 2011), compared to younger adults. This suggests that with aging, fewer cognitive resources are available to allocate attention to a secondary task. Indeed, neuroimaging evidence shows increased prefrontal cortex activity during dual-task compared to single-task walking, suggesting that more cognitive resources are required for complex gait (Holtzer et al., 2014; Mirelman et al., 2017).

Moreover, according to the posture-first hypothesis, when given instructions to equally prioritize both the motor and cognitive task during dual-tasking, older adults prioritize walking, showing greater DTCs in the cognitive domain, while younger adults show more even emphasis across tasks (Li et al., 2001; Verghese et al., 2007). This asymmetry might be due to the greater survival value attributed to walking in old age, thereby leading to greater priority, as compared to the simultaneous cognitive task performance. Together, these findings suggest that age-related declines in cognitive capacity play an increasing role in gait with aging. Interventions aimed at enhancing cognitive capacity in older adults may therefore be critical for improving cognitive-motor dual-tasking.

The extant literature suggests that computerized EF training leads to near-transfer effects, such as inhibitory control, divided attention, and task-switching (Desjardins-Crepeau et al., 2016; Bherer et al., 2021a) as well as far-transfer effects including dual-task balancing (Li et al., 2010; Smith-Ray et al., 2015) and walking (Verghese et al., 2010; Smith-Ray et al., 2015; Fraser et al., 2017). Such improvements to motor performance after cognitive training are attributed to the increase in cognitive resources available for dividing one's attention between the cognitive and motor tasks (Li et al., 2018).

Aerobic exercise (AE) has also been associated with enhanced EF (e.g., inhibition and working memory; Colcombe and Kramer, 2003), brain plasticity (Erickson and Kramer, 2009; Weinstein et al., 2012), and dual-task walking and balance (Fraser et al., 2017). Stillman et al. (2016) propose a conceptual model for possible mechanisms of physical activity in mediating neurocognitive functioning, including cellular and molecular changes, which initiate macroscopic changes to the brain and behavior, that, in turn, influence cognition. The cardiovascular hypothesis, which is one component of the model, suggests that aerobic capacity or cardiovascular efficiency may mediate improvements in executive functioning, which could increase cognitive resources required during dual-task processing (Stillman et al., 2016). Indeed, recent research has shown that in older adults, increased cardiorespiratory fitness mediated the improvements seen in processing speed for older-old adults, and task-set costs (i.e., the ability to maintain different response alternatives in memory and prepare to answer multiple tasks) in younger-old adults following AE (Bherer et al., 2021b). Moreover, increased cardiorespiratory fitness may improve dual-task walking performance by decreasing the relative intensity of the walking task for a given gait speed. This, in turn, may reduce the demands of executive control during dual-tasking and allow more attention to be allocated to the cognitive task.

Gross motor abilities training (GMA), also termed *coordination training*, has shown far transfer effects in improving cognitive processes such as executive control and processing speed, as well as decreasing prefrontal activity, suggesting more efficient information processing (Voelcker-Rehage et al., 2011). GMA training has also been shown to improve inhibitory control under single (Forte et al., 2013) and dual-task conditions, as well as maximum walking speed (Berryman et al., 2014). According to this framework, gait impairments observed in older adults are suggested to be due in part to altered coordination, which increases the amount of energy required to walk due to motor inefficiency (Van Swearingen and Studenski, 2014). Therefore, improvements in dual-task performance following GMA training are suggested to be due to increased coordinated walking abilities, thereby reducing the energy cost of walking (ECW). In turn, this would reduce the relative intensity of the walking task and allow for more resources to be allocated to the cognitive domain. Together, this research suggests that EF, AE, and GMA training have a strong potential to improve cognitive-motor dual-task performance, which may be mediated by different underlying mechanisms.

As previously mentioned, comparisons of interventions on cognitive-motor dual-task performance in older adults show similar improvements across groups, providing evidence for a multiple routes perspective. Specifically, Berryman et al. (2014) found similar improvements in cognitive performance during a dual-task condition following either combined resistance with AE training or GMA training. Moreover, in a study contrasting different combinations of active training conditions (EF, AE) and active control conditions (computer lessons, stretching), comparable dual-task improvements were found across the active training groups, including dual-task walking speed, balance (Fraser et al., 2017), and functional mobility (Desjardins-Crepeau et al., 2016). Finally, Pothier et al. (2021) found that global mobility (i.e., Timed up and Go) improved to a similar extent in older adults following either EF, AE, or GMA training. However, no research to date has compared the effect of these three well-established training approaches on cognitive-motor dual-task performance in healthy older adults.

In summary, older adults have poorer dual-task performance compared to younger adults, which is in part due to reduced cognitive resources and motor alterations (Van Swearingen and Studenski, 2014; Stillman et al., 2016; Li et al., 2018). Although there is substantial evidence to suggest that certain interventions may help maintain or improve dual-task performance in older adults, there is limited research directly comparing EF, AE, and GMA training. We therefore sought to investigate the effects of (i) EF (ii) AE, and (iii) GMA training on cognitive-motor dual-tasking in older adults and to examine the mechanisms underlying each intervention using a proof of concept study design.

We hypothesized that (1) following training, there would be a greater reduction in cognitive dual-task costs (DTCs) compared to gait DTCs. Based upon the posture-first hypothesis, that older adults tend to exhibit greater DTCs to cognitive performance than to walking (Li et al., 2001), there is greater potential for cognitive improvement than motor improvement. We also anticipated that (2) all participants, regardless of the training arm, would have similar improvements in cognitive DTCs following training, based upon previous research findings of null group differences on dual-task costs (i.e., 3). In order to verify the intended underlying mechanisms of the interventions, we hypothesized that (3) the different training arms would lead to specific improvements in: (i) EF following EF training, (ii) cardiorespiratory fitness (i.e., VO_{2peak}) following AE, and (iii) ECW following GMA. This hypothesis was grounded in research on the proposed mechanisms of each intervention (Van Swearingen and Studenski, 2014; Li et al., 2018; Bherer et al., 2021b), as well as a joint study from our laboratory that used the same training design, but assessed functioning mobility rather than cognitive-motor dual-tasking (Pothier et al., 2021).

Materials and methods

Participants

A total of 125 community-dwelling older adults were first recruited and assessed for eligibility. Thirty participants did not meet inclusion criteria at the time of enrollment, resulting in 95 participants being randomized to each of the three training arms. A total of 17 participants abandoned the intervention voluntarily before its completion (6 from EF: study too demanding = 1, sickness/health issues = 2, no longer interested = 2, too many absences = 1; 6 from AE: study too demanding = 1, sickness/health issues = 2, no longer interested = 3; 5 from GMA: study too demanding = 1, sickness/health issues = 2, no longer interested = 1, involved in another parallel study = 1). Due to data-registration issues concerning the dual-task data for the first six cohorts, we have opted to report only the data for the subsequent cohorts after the problem was addressed. This resulted in a subset of 33 participants (EF = 10, AE = 10, GMA = 13) that were included in the present analyses (see Figure 1 for CONSORT diagram). There were no significant differences between groups in terms of attendance and drop-out rates, suggesting similar adherence across groups. There were also no significant differences in the participant characteristics between participants who had complete data and were analyzed for this study compared to participants who had missing data (see Table 1). Finally, results from Little's MCAR test showed that the data were missing completely at random, $\chi^2(21) = 23.40$, $p = 0.323$. These findings suggest that the subset of participants is representative of the full dataset and that the data are not biased.

A statistical power analysis was performed for sample size estimation, based on published data (Fraser et al., 2017) which compared n-back accuracy and walking speed before and after 12 weeks of different combinations of AE, EF, and placebo controls. The effect sizes for the main effect of Time in this study (n-back accuracy: $n^2 = 0.11$; walking speed: $n^2 = 0.29$) are considered to be large using Cohen's (Cohen, 1988) criteria. With an alpha set at.05 and power set at 0.95, the projected sample size needed to find a significant main effect of Time with this effect size (G*Power 3.1) is approximately n = 30. Accounting for possible attrition (20%), a total of n = 36 participants is required. Thus, our final sample size of n = 33 is adequate for the main objective of this study. We also provide effect sizes to support the strength of the observed findings.

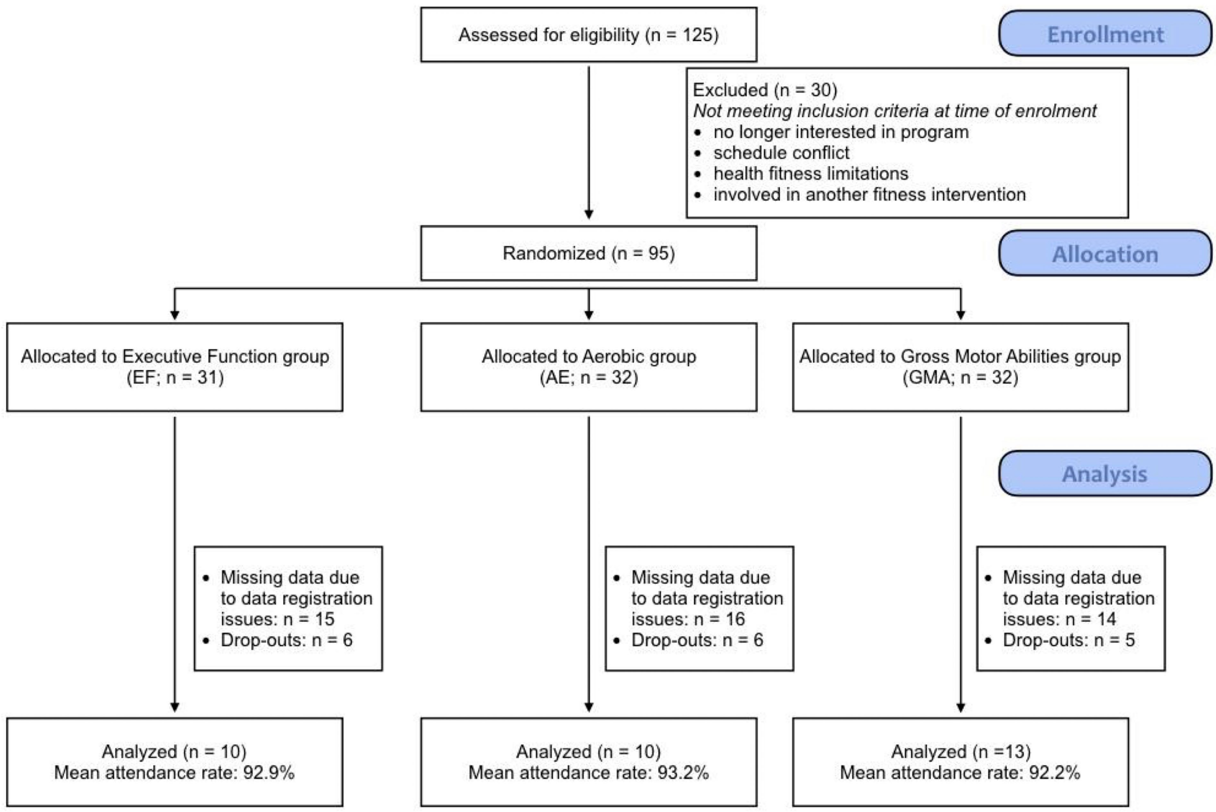

FIGURE 1
CONSORT flow diagram. Note: The final row depicts the number of participants included in the study.

Nevertheless, we recognize that the small sample size due to data-registration issues is a limitation of the study.

Eligible participants were 60 years or older, able to speak fluently, and comprehend either English or French, and were not on medications that could impair their cognitive and physical test performance. Participants were excluded if they participated in a structured training program over the last year, failed the assessment of readiness to exercise (PAR-Q+; Thomas et al., 1992), or had a chronic medical condition such as cardiopulmonary or musculoskeletal diseases, neurological disease, or early signs of dementia (<26 on the Mini-Mental State Exam: MMSE; Folstein et al., 1983), depression (≥11 Geriatric Depression Scale; Brink et al., 2013), or major uncorrected perceptual limitations. Participant characteristics by treatment group are shown in Table 2. All participants provided informed consent as approved by the Institut Universitaire Gériatrie de Montreal Ethical Research Committee and Concordia University's Human Research Ethics Committee.

Procedure

Participants were first screened for eligibility with a phone interview and then a medical evaluation by a geriatrician. Eligible participants completed a pre-test evaluation of cognitive and physical measures, including the dual-task assessment. Participants were then randomized into one of three training protocols: EF, AE, or GMA, which consisted of three, 1-h sessions a week, for 12 weeks (completed in small groups of 5–8 individuals). Within 3 weeks after training, participants completed a post-test evaluation using the same measures.

Measures

In addition to the tests described below, other outcome measures (e.g., global mobility, neuropsychological functioning) were administered to the larger sample and are presented elsewhere (Pothier et al., 2021; Vrinceanu et al., 2022).

Background measures

Cognitive functioning was screened using the MMSE (/30; Folstein et al., 1983) and Montreal Cognitive Assessment (MoCA; /30; Nasreddine et al., 2005). While a MoCA score below 26 can be indicative of mild cognitive impairment, participants who scored below this were still included if they performed above the

TABLE 1 Dual-task costs before and after training across groups.

		Cognitive DTC (%)			Walking DTC (%)		
		Mean (SD)	*F*	*p*	Mean (SD)	*F*	*p*
Between-subjects effects							
Group	EF	0.90 (9.77)	4.36	0.022*	−2.29 (7.41)	0.928	0.839
	AE	2.96 (9.77)			1.62 (7.41)		
	GMA	−8.22 (9.77)			1.47 (7.41)		
Within-subjects effects							
Time	Pre-training	3.89 (12.8)	8.82	0.006*	0.917 (7.45)	0.618	0.438
	Post-training	−8.03 (17.5)			−0.16 (10.1)		
Time x Group	EF Pre-training	7.49 (15.5)	0.169	0.845	−1.38 (8.18)	0.911	0.413
	EF Post-training	−5.70 (11.7)			−3.20 (9.55)		
	AE Pre-training	7.19 (10.5)			3.53 (8.36)		
	AE Post-training	−1.27 (14.1)			−0.30 (11.0)		
	GMA Pre-training	−1.41 (11.2)			0.67 (5.95)		
	GMA Post-training	−15.0 (21.8)			2.27 (9.90)		

DTC = dual-task cost as derived by [(ST − DT)/ST] * 100. There was a significant reduction in cognitive DTCs following training (negative score indicates dual-task facilitation, such that cognitive accuracy was better during dual-tasking, compared to single-tasking), with no significant change in walking DTCs following training.

TABLE 2 Demographic information and baseline cognitive and physical capacity across training groups for participants included in the statistical analyses and participants who were not due to missing data.

Characteristic	Analyzed data			Missing data		
	EF	AE	GMA	EF	AE	GMA
	n = 10	*n* = 10	*n* = 13	*n* = 16	*n* = 14	*n* = 14
Age (years)	70.0 (6.09)	68.2 (5.34)	70.2 (3.85)	70.4 (5.43)	69.1 (4.49)	70.7 (5.30)
Sex (*n*, % male)	7 (70.0)	4 (40.0)	5 (38.5)	5 (29.4)	3 (20.0)	5 (31.3)
Education (years)	16.2 (2.70)	18.0 (4.55)	17.4 (5.30)	15.1 (4.31)	15.29 (2.64)	15.0 (2.16)
MoCA	25.4 (2.55)	27.7 (1.89)	25.2 (2.66)	26.4 (2.72)	26.6 (2.59)	26.4 (3.45)
MMSE	28.3 (1.51)	28.5 (1.58)	28.7 (1.21)	28.4 (0.84)	28.7 (1.27)	28.3 (1.50)
TUG (sec.)	9.18 (1.34)	7.79 (1.36)	9.20 (1.40)	9.36 (1.51)	8.80 (1.32)	9.30 (1.86)

MoCA = Montreal Cognitive Assessment, MMSE = Mini-Mental State Exam, TUG = Timed Up and Go. Values indicate means and standard deviations in brackets. There were no significant differences across training groups, suggesting that randomization was appropriate. There were no significant differences between participants included in the main statistical analyses and those who were not due to missing data, suggesting that the participant characteristics of the smaller dataset are representative of the full dataset.

clinical cut-off on the MMSE (i.e., 26). Global mobility was also assessed using the Timed Up and Go (TUG) task (Shumway-Cook et al., 2000).

Primary outcome measures

Cognitive task

An auditory 2-back task (Fraser et al., 2017) served as the cognitive outcome measure in single- and dual-task conditions. In the single-task condition, participants performed the 2-back task while standing. In the dual-task condition, they performed the task while walking (see below). Randomly ordered single digits were presented through a set of wireless headphones (Sennheiser Canada, Pointe-Claire, QC, Canada) at a 2-s rate, for a total of 30 s. Participants were asked to recall out loud the number they heard two items previously (2-back). The responses were manually recorded during each trial, then converted to accuracy scores (% correct out of 15). *Walking Task.* Participants were instructed to walk around a 23-meter oval track, demarcated by a single stretch of tape on the floor, at their normal walking speed. Each walking trial was initiated by the audio signal, "GO," heard through wireless headphones, and ended with the audio signal, "STOP." Each trial lasted 30 s. The distance walked was manually recorded and divided by 30 s to attain a measure of gait speed (m/s). *Dual-Task.* Participants completed the 2-back cognitive task while concurrently walking at a self-selected pace. They were instructed to perform both the cognitive and walking task equally well.

Participants were first familiarized with each of the single tasks before introducing the dual-task procedure. Feedback on performance was only given during the familiarization portion of the task. Each block consisted of three trials (single-task 2-back, single-task walk, and dual-task), which were repeated across four blocks. Dual-task costs (DTC; %) were calculated as: [(single-task – dual-task)/single task * 100], for cognitive accuracy (i.e., cognitive DTCs) and gait speed (i.e., walking DTCs; greater positive number indicates poorer performance when completing the dual-task compared to single-task). DTC change scores were calculated by subtracting the post-training DTCs from the pre-training DTCs (greater negative number indicates more improvement following training).

Secondary outcome measures

In addition to the primary experimental outcomes, three indexes were included to address the underlying mechanisms associated with each training type and assessed during pre-and post-training phases so that the *magnitude of change* in executive function, aerobic capacity, and motor skills could be quantified and considered as potential predictors of change in dual-task walking.

Changes in executive function

Changes in executive functions due to training were measured using a variant of the Stroop task used during training. Instead of using letters, the pre-and post-intervention variant involved digits. The assessment comprised five different conditions (familiarization, reading, counting, inhibition, and switching); however, reaction times for the inhibition and switching trials were analyzed as potential mechanisms underlying the EF training as these tasks rely most heavily on executive function. In the inhibition condition, digits were presented on the screen, whereby the number of digits was incongruent with the digit displayed (e.g., five number twos were presented). Participants were instructed to identify the quantity of digits presented, while inhibiting responses indicating the digits that were displayed on the screen. In the switching condition, the stimuli were identical to those in the inhibition condition, except that on some trials, the digits were surrounded by a white frame, to indicate a goal switch, whereby participants had to identify the digit that was presented on the screen, rather than indicating the quantity of digits.

Changes in cardiorespiratory fitness

The proposed mechanism thought to underlie the AE training protocol was cardiorespiratory fitness, as measured by peak oxygen uptake (VO_{2peak}). The detailed protocol has been described previously (Berryman et al., 2013). Briefly, participants wore an electrocardiogram to monitor heart rate and a mask to measure gas exchange during a maximal graded exercise test on a cycle ergometer. The test began at a pre-defined load and then increased in workload by 15 Watts. Testing was completed when participants reached exhaustion (i.e., were unable to maintain the cadence of 60 to 80 revolutions per minute) or according to reasons described by the ASCM (American College of Sports Medicine, 2001). VO_{2Peak} was defined as the highest volume of oxygen consumed over a 30 s interval in $ml.kg^{-1}.min^{-1}$.

Change in the energy cost of walking

The mechanism thought to underlie the GMA training protocol is the energy cost of walking (ECW). All participants were equipped with the same mask to measure the O_2 consumption and CO_2 production as during the VO_{2Peak} assessment. However, participants walked on the treadmill during 6 min at a constant speed of $4\,km.h^{-1}$. The oxygen cost of walking (OCW), in $ml.kg^{-1}.min^{-1}$, represents the mean VO_2 from the last 2 min of the walking task. The ECW was calculated as described elsewhere (Berryman et al., 2012). Briefly, the gross OCW ($ml.kg^{-1}.min^{-1}$) was divided by the walking speed ($m.min^{-1}$) to obtain a value in $ml.kg^{-1}.m^{-1}$. Thereafter, values in $ml.kg^{-1}.m^{-1}$ were first converted into $L.kg^{-1}.m^{-1}$. Using the respiratory exchange ratio (RER) corresponding to the last 2 min of walking, an appropriate energy equivalent of oxygen ($J.L^{-1}$) was used to convert the previously calculated ECW ($L.kg^{-1}.m^{-1}$) in $J.kg^{-1}.m^{-1}$. RER had to be below 1 during the last 2 min of walking so that oxygen values could be considered for further analyses. These procedures are in agreement with the scientific literature for moderate-intensity exercise (Xu and Rhodes, 1999; Fletcher et al., 2009).

Training protocol

Executive function training

The EF intervention was completed on individual tablets while seated. Participants completed three executive function tasks per session: (i) visual n-back, (ii) Stroop, and (iii) dual-task (20 min/task).

The n-back task was designed to improve updating. Participants were required to indicate whether the current number presented matched the number from *n steps* earlier in the sequence (Kirchner, 1958). The stimuli included numbers between "1" to "9." Reaction times (ms) and accuracy (total number correct/ maximum possible correct) were recorded. Difficulty levels were incremented over the 3 months of training (from 1-back to 3-back).

The modified Stroop task was designed to improve inhibition and switching and was comprised of five different conditions (familiarization, reading, counting, inhibition, and switching). In the familiarization condition, participants were required to press a button corresponding to the digit presented on the screen ("1" to "3" with their left thumb, "4" to "6" with their right thumb). In the reading condition, multiple identical digits were presented in a small group, where the identity of the digit corresponded with the quantity of the digits presented (e. g., four copies of the digit "4"), and participants had to press the corresponding button with their thumb. In the counting condition, groups of one to six asterisks were presented and the participants had to report how many asterisks were present. In the inhibition condition, letters were presented in small identical groups; however, the letters presented were incongruent with the larger letter that was formed (e.g., copies of small letters "L" to form a big "H"). Participants were instructed to identify the larger formed letter, while avoiding responses to the small grouped letters. In the switching condition, the stimuli were identical to those in the inhibition condition, except that on some trials, the group of small letters was surrounded by a white frame, to indicate a goal switch, whereby participants had to identify the small letters instead of the bigger formed letter for those trials only.

The dual-task program was designed to improve divided attention by having participants perform two discrimination tasks either alone or simultaneously. Stimuli were presented either visually (e.g., fruits vs. modes of transport; letters vs. numbers) or orally (sounds vs. beeps) using headphones. Participants completed blocks of single-task trials (Pure blocks) or mixed trials that randomly involved one or both tasks (Single-mixed trials and Dual-mixed trials, respectively). For Dual-mixed trials, participants were instructed to respond to both stimuli equally. However, after two training sessions, participants were encouraged to prioritize one hand over the other to increase the level of difficulty (i.e., in the dual-mixed trials when two stimuli were presented, participants were asked to make a response using their left or right hand first before making a response with the other hand).

Aerobic exercise training

The AE training involved recumbent cycling designed to enhance cardiorespiratory fitness and aerobic endurance. Each training session alternated between high-intensity interval exercises and moderate-intensity continuous exercises. Such a program was previously implemented and led to significant improvements in cardiorespiratory fitness (Berryman et al., 2014). Maximal Aerobic Power (MAP) was measured at baseline and represents the highest mechanical power output (Watts) produced by participants at the end of a maximal graded test performed on a cycle ergometer (Lode, CORIVAL). Participants began at a pre-defined starting workload for women (35 Watts) and men (50 Watts). The workload then increased by 15 Watts until exhaustion. Participants were required to maintain a pedaling rate of 60 to 80 revolutions per minute. Testing was completed when participants were unable to maintain the cadence or according to reasons described by the American College of Sports Medicine (American College of Sports Medicine, 2001). This information was used to calibrate individualized workload for the AE training.

Each training session included a 10-min warm-up, during which participants maintained 50% of their MAP. For the HIIT sessions, the warm-up was followed by two 5-min intervals, during which participants alternated between 15 s bouts of cycling at 100% MAP, with recovery at 60% MAP. For the continuous low-intensity training, the warm-up was followed by 20 min of cycling at 65% MAP. Every session ended with a 10-min cool-down period at 50% of their MAP. The intensity of the continuous aerobic exercise was increased individually according to each participant's MAP by 5% after each month, with all participants increasing to 75% MAP at the end of training for the continuous low-intensity training and 110% MAP for the HIIT training.

Gross motor abilities training

The GMA training protocol was adapted from a previous study [see 2 for detailed protocol]. Briefly, participants started each session with a low-intensity walking exercise on a treadmill at a self-selected pace for 10 min (max. 2.5 km/h, 1% incline). Participants then completed different exercises designed to improve coordination, balance, and agility for approximately 30 min (e.g., walking over obstacles, standing on one foot, and juggling lessons). As the intervention progressed, exercises combining multiple skills (coordination, agility, and balance) were added to increase the level of difficulty (e.g., maintaining balance on one foot and throwing a ball in a box). Participants then completed another 10 min of low-intensity walking on a treadmill. Each session concluded with five minutes of stretching and relaxation exercises.

Statistical analyses

All data analyses were completed using IBM SPSS Statistical Software version 26. The data were screened for normality, outliers, and missing values. To evaluate the effectiveness of randomization to groups, one-way ANOVAs were carried out using each of the background measures and key outcome measures (single- and dual-task gait speed and 2-back accuracy) collected prior to the training phase. To evaluate the dual-task manipulation at baseline, paired sample t-tests were carried out on single- and dual-task gait speed and cognitive accuracy using the pre-training assessment data.

Two 2 × 3 Mixed Factorial ANOVAs were then conducted on each of the DTC scores (Cognitive, Walking) to assess change from pre-to post-training across training arms, where the within-subjects effect was Time (pre-vs. post-training) and the between-subjects effect was Training Group (EF, AE, GMA). A set of 2 × 3 ANOVAs were then conducted for each of the potential mechanisms underlying the training arms (Stroop inhibition and switching RT, CRF, and ECW) to assess the within-subjects effect of Time (pre-vs. post-training) and the between-subjects effect of Training Group (EF, AE, GMA). All follow-up analyses were Bonferroni corrected. In order to ensure that the results were not influenced by regression to the mean, all significant ANOVAs were followed up with an ANCOVA, where the covariate was the baseline score on the outcome measure found to be significant. Effect sizes were calculated as Hedges' *g* for the t-tests and ANOVAs to account for small sample size, with the magnitude of effect being considered small ($0.2 < ES \leq 0.5$), moderate ($0.5 < ES \leq 0.8$), or large ($ES > 0.8$).

Results

Baseline group differences

Results revealed no significant differences ($ps > 0.05$) between groups for any of the background measures (i.e., age, sex, education, MoCA, MMSE, and TUG) or key experimental measures in the pre-training phase, suggesting that randomization was effective (Table 2).

Baseline single- and dual-task performance

No significant differences between single- and dual-task conditions were found in performance on cognitive accuracy [$t(32) = 1.58$, $p = 0.123$], or gait speed [$t(32) = 0.66$, $p = 0.514$] at baseline. While not significant, it is notable that the range of scores was quite large, particularly for the single-task ($SD = 19.49\%$) and dual-task ($SD = 18.90\%$) cognitive accuracy data.

To understand the large range of cognitive task performance, we examined global cognitive status as an individual differences factor as a possible influence. Specifically, we conducted two *post-hoc* One-Way ANOVAs on single- and dual-task cognitive accuracy scores, splitting participants between low (i.e., MoCA score < 26; $n = 14$) or high cognitive status (i.e., MoCA ≥26; $n = 18$). Results showed that participants with lower MoCA scores at baseline had significantly lower cognitive accuracy under single- [$F(1, 31) = 10.8$, $p = 0.003$] and dual-task conditions [$F(1, 31) = 10.9$, $p = 0.002$], compared to participants with higher MoCA scores. Notably, there were no significant age differences between low versus high MoCA scorers.

Training effects

Regarding walking DTCs, there was no significant effect of Time, $F(1, 30) = 0.618$, $p = 0.438$, $g = -0.11$), with DTC scores remaining similar following training ($M = -0.16\%$) compared to baseline ($M = 0.92\%$). There was also no significant effect of Group ($p = 0.406$), nor a significant Time by Training Group interaction ($p = 0.369$).

For the cognitive DTCs, there was a significant main effect of Time, $F(1, 30) = 8.82$, $p = 0.006$, g:−0.83 (large effect size; Figure 2), indicating diminished DTCs following training, such that dual-tasking became facilitative after training ($M = -8.03\%$), compared to baseline ($M = 3.89\%$). There was also a significant main effect of Training Group, $F(1, 30) = 4.36$, $p = 0.022$, irrespective of Time. Follow-up pairwise comparisons revealed that the GMA group had significantly lower cognitive DTCs ($M = -8.22\%$) compared to the AE group ($M = 2.96\%$), $p = 0.032$. However, there was no significant interaction effect of Time and Training Group ($p = 0.845$), suggesting that all groups improved similarly. Indeed, a follow-up One-Way ANOVA comparing the change in cognitive DTCs from pre-to post-training across groups was non-significant ($p = 0.943$), and effect sizes showed similar rates of improvements across groups (g: EF: −0.91 [large effect], AE: −0.65 [moderate effect], GMA: −0.76 [moderate effect]). Results from the ANCOVA, where the between-subjects factor was Training Group and the covariate was baseline cognitive DTC scores, showed similar findings as our primary analysis, such that that the cognitive DTC change scores did not significantly differ across groups, $F(2, 29) = 2.46$, $p = 0.104$, suggesting that the results are not due to a regression to the mean.

Given the unusual finding that the cognitive accuracy DTCs became better during walking (dual-task facilitation) after training, we sought to better understand this effect using *post-hoc* individual differences analyses. As mentioned, there was large variability in 2-back performance that was influenced by baseline cognitive status as measured with the MoCA. Therefore, we compared post-training cognitive DTCs across those with low (i.e., MoCA score < 26, $n = 14$) versus high cognitive status (i.e., MoCA ≥26, $n = 18$) using a One-Way ANOVA. Results showed a significant difference between groups, such that low MoCA scorers at baseline were more likely to have a dual-task facilitative effect post-training ($M = -14.9$, $SD = 16.9$), compared to high MoCA scorers, who showed negligible dual-task costs post-training ($M = -0.17$, $SD = 11.7$), $F(1, 31) = 8.52$, $p = 0.007$ (see Figure 3 for single- and dual-task scores before and after training between low vs. high MoCA scorers). To further investigate if this result was due to a regression to the mean, we conducted an ANCOVA, where the between-subjects factor was MoCA status (i.e., low vs. high scorers) and the covariate was baseline cognitive DTC scores. Results showed similar results to our initial One-Way ANOVA, such that the cognitive DTC change scores were significantly greater in the low MoCA scorers compared to the high MoCA scorers, $F(1, 29) = 5.303$, $p = 0.029$, suggesting that the results are not significantly influenced by regression to the mean.

Given the cognitive accuracy dual-task facilitation following training, we wondered whether attentional allocation to the walking task differed across participants with low versus high cognitive status. Results from the *post-hoc* One-Way ANOVA showed no significant differences in post-training walking DTCs between participants with low ($M = 3.16$ $SD = 9.98$) versus high baseline cognitive status ($M = -2.87$, $SD = 9.88$), $F(1, 31) = 2.91$, $p = 0.10$.

Mechanisms underlying dual-task improvements

Executive function

A significant effect of Time, $F(1, 30) = 30.3$, $p < 0.001$, and a Group by Time interaction, $F(1, 30) = 13.2$, $p = 0.001$, was found for the Stroop inhibition condition, with reaction times only decreasing for the EF group; g: EF = −0.96 [large effect] Δ = −14.8%; AE = −0.11 [no effect], Δ = −1.90%; GMA = −0.12 [no effect], Δ = −2.49%; Figure 4. Similarly, in the switching

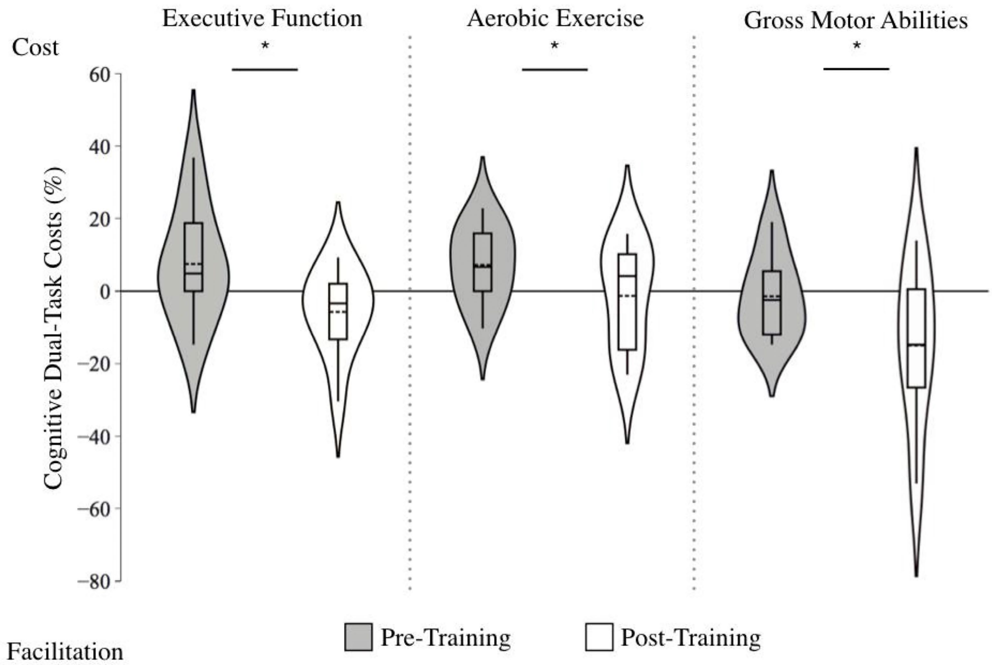

FIGURE 2
Violin plot of cognitive dual-task costs before and after training across training groups. Note: Positive scores indicate greater dual-task costs (i.e., lower 2-back accuracy during dual-tasking compared to single tasking), whereas negative scores indicate dual-task facilitation (i.e., higher 2-back accuracy during dual-task compared to single task). The length of each curve represents the range of scores, the width represents the frequency of data points in each region, the solid line within each boxplot represents the median, and the dotted line represent the mean. Following training, cognitive accuracy dual-task costs improved, regardless of the training protocol (g=−0.83).

condition, there was a significant effect of Time [F (1, 30) = 23.4, p < 0.001], as well as a Group by Time interaction, F (1, 30) = 13.5, p < 0.001, whereby only the EF group showed improvement, F (1, 25) = 9.18, p < 0.01; g: EF = −1.59 [large effect], Δ = −25.8%; AE = −0.05 [no effect], Δ = −0.98%; GMA = −0.25 [small effect], Δ = −4.30%; Figure 5.

Cardiorespiratory fitness

There was no significant effect of Time, F (1, 30) = 1.94, p = 0.174, though there was a Group by Time interaction that approached significance, F (1, 30) = 3.23, p = 0.054. A *post-hoc* One-Way ANOVA comparing the change in VO_{2Peak} across training groups was significant, F (1, 30) = 3.70, p = 0.037, with the AE group improving the most; AE: g = 0.31 [small effect] Δ = 9.07%; EF: g = −0.001 [no effect], Δ = −0.05%; GMA: g = −0.07 [no effect], Δ = −1.98%; Figure 6. Also notable is how the AE group had the highest baseline VO_{2peak} (M = 24.0, SD = 7.10), compared to EF (M = 21.9, SD = 6.48) and GMA (M = 19.9, SD = 5.84).

Energy cost of walking

There was a main effect of Time that approached significance, F (1, 30) = 3.85, p = 0.059, with ECW decreasing following training. There was no significant Group by Time interaction, F (1, 30) = 1.86, p = 0.175. However, the ECW was found to decrease the most in the GMA group: g: GMA = −0.94 [large effect], Δ = −11.0%; EF = −0.13 [no effect], Δ = −1.93%; AE = −0.07 [no effect], Δ = −1.15%; Figure 7.

Discussion

We aimed to evaluate the effect of cognitive training, aerobic exercise, and gross motor training on cognitive accuracy and gait speed under single- and dual-task conditions in healthy older adults. Notably, compared to pre-training levels, cognitive DTCs improved, switching to dual-task facilitation, regardless of the training modality (i.e., similar magnitudes of improvement following either cognitive or physical interventions), whereas no training effects were observed in gait speed DTCs. To better understand how various interventions have led to similar improvements in dual-task performance, we also investigated potential mechanisms specific to each training protocol. We found significant improvements in EF for participants in the cognitive training group alone, as well as larger improvements in cardiorespiratory fitness for participants in the aerobic exercise group, and greater reductions in metabolic energy demands of walking for participants in the gross motor training group. These findings are consistent with a recent study from our laboratory which had a larger sample size, showing comparable improvements in global mobility following the three interventions (Pothier et al., 2021).

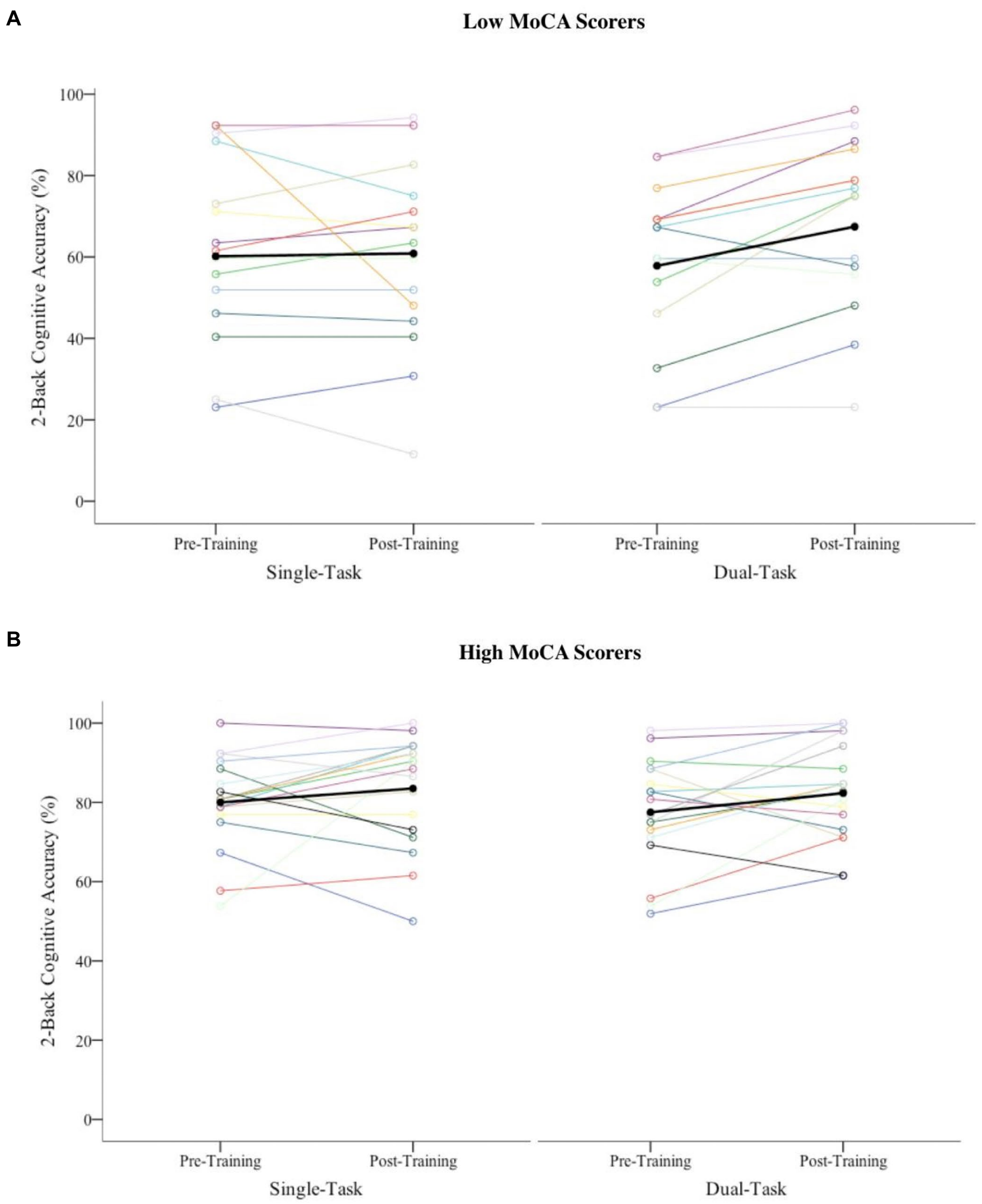

FIGURE 3
Single- and dual-task cognitive accuracy performance before and after training across participants with low versus high MoCA scores. Note: **(A)** Low baseline MoCA scorers (i.e., <26; *n* =14), **(B)** high Low baseline MoCA scorers (i.e., ≥26; *n*=18). Each line represents an induvial participant score (black line indicates the mean). While the high MoCA scores have the highest accuracy before and after training, there is greater improvement in the single to dual-task cost ration in low MoCA scores, leading to dual-task facilitation.

Greater improvements in cognitive vs. gait DTCs

The finding of greater improvements in cognitive DTCs compared to gait DTCs following training is consistent with our first hypothesis, which was based upon the postural prioritization hypothesis (Li et al., 2001). Specifically, since older adults tend to prioritize walking performance over cognitive accuracy during dual-tasking due to its heightened survival value, we expected there would be a greater opportunity for improvement in cognitive DTCs. Very notably, the improvements in cognitive DTCs became facilitative, meaning that cognitive accuracy became better while walking compared to while standing. However, this did not come at a decrement to gait performance.

To better understand the dual-task facilitative effect, *post-hoc* analyses were conducted, comparing dual-task performance across participants with varying levels of cognitive ability, as measured by the MoCA. First, we demonstrated that older adults with lower MoCA scores (i.e., < 26 – the clinical cut-off for mild

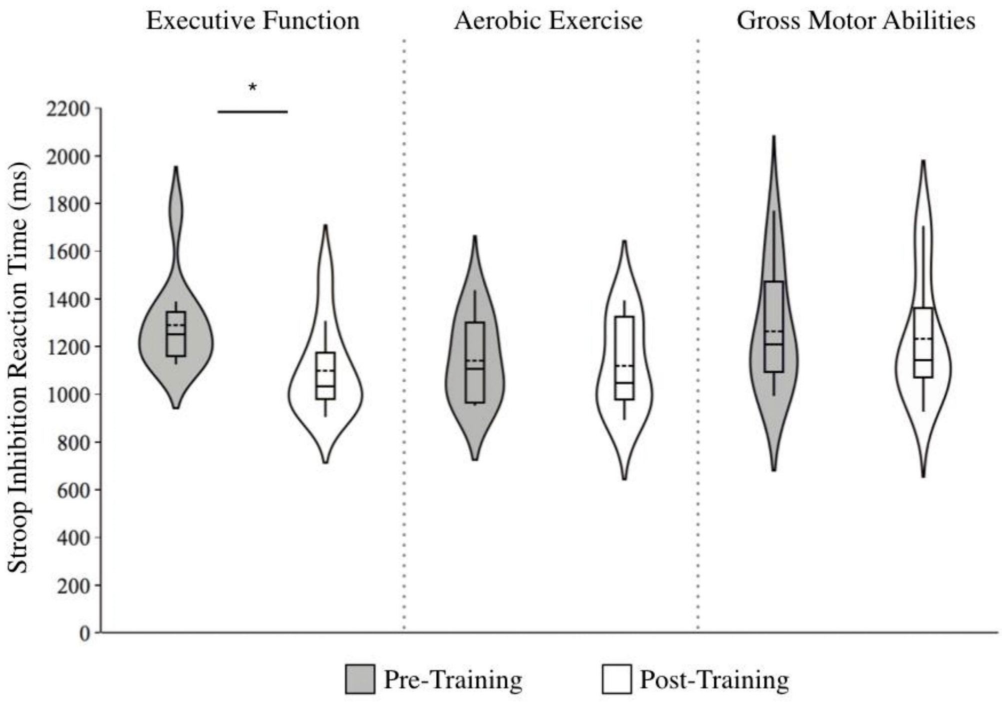

FIGURE 4
Violin plots of Stroop inhibition reaction times before and after training across training groups. Note. Lower scores indicate faster responses. The length of each curve represents the range of scores, the width represents the frequency of data points in each region, the solid line within each boxplot represents the median, and the dotted line represent the mean. There were significant improvements in reaction time for the executive function training group alone (g =−0.96 [large effect], Δ=−14.8%).

cognitive impairment), had poorer baseline 2-back accuracy under both single and dual-task conditions. While this was expected, we did not anticipate our next finding, which was that post-training, participants with low baseline cognitive status had cognitive dual-task facilitation, whereas participants with high baseline cognitive status scores had negligible dual-task costs.

We had instead expected that older adults with high MoCA scores might have few DTCs at baseline and would be more likely to show dual-task facilitation post-training, whereas older adults with low MoCA scores might have greater costs at baseline, which would become negligible post-training. This expectation was based upon research by Wollesen and Voelcker-Rehage (2018), who demonstrated that older adults with greater physical functioning (i.e., handgrip strength) had facilitative dual-task performance in their walking speed (i.e., walked faster while doing a cognitive task than when walking alone). In contrast, older adults with lower physical functioning exhibited greater dual-task costs. Moreover, in the cognitive literature, mnemonic training has been shown to magnify individual differences based on age and baseline performance. Specifically, younger participants and those with higher baseline performance tend to have greater mnemonic gains following training (Baltes, 1987; Lövdén et al., 2012).

Although in our study participants with higher baseline MoCA scores did not have the facilitative effect as predicted, we did show that they had negligible DTCs both before and after training, which may suggest efficient complex walking behavior. For participants with lower cognitive status at baseline, an increase in cognitive resources following the intervention may have allowed greater attentional allocation to the cognitive task, leading to dual-task facilitation, while maintaining walking performance. The observed dual-task facilitation in cognitive accuracy thus appears to be driven by the proportion of older adults with lower cognitive status. This finding has direct clinical implications for older adults with low cognitive status as it demonstrates that either cognitive or physical interventions can improve cognitive efficiency during complex walking, which may reduce risk of falling and cognitive decline.

One important limitation to consider when interpreting these results is the lack of a control group, which makes it difficult to conclude whether the improvements observed in cognitive DTCs were not solely due to re-test effects. As this study followed a proof of concept design, the aim was to directly compare three well-established intervention protocols that have shown to be effective in improving cognitive or motor functioning in older adults. Indeed, EF and AE training have been shown to lead to greater improvements in executive functioning (e.g., DTCs on a computerized divided attention task, Stroop switching reaction time) compared to a placebo control group (Desjardins-Crepeau et al., 2016; Fraser et al., 2017; Bherer et al., 2021a). Single- and dual-task walking speed have also been shown to improve more following EF training compared to a wait-list control group

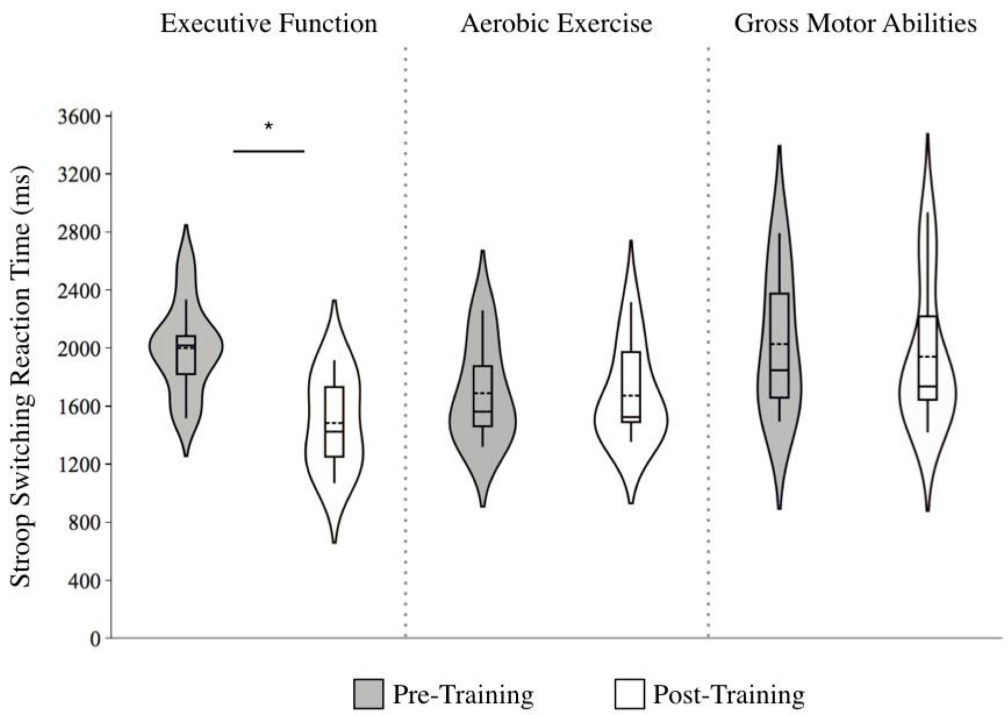

FIGURE 5
Violin plot of Stroop switching reaction times before and after training across training groups. Note: Lower scores indicate faster responses. The length of each curve represents the range of scores, the width represents the frequency of data points in each region, the solid line within each boxplot represents the median, and the dotted line represent the mean. There were significant improvements in reaction time for the executive function training group alone (g=−1.59 [large effect], Δ=−25.8%).

(Verghese et al., 2010). GMA training has also been shown to improve executive control and processing speed more than a placebo control group (Voelcker-Rehage et al., 2011). These studies highlight the effectiveness of the chosen interventions for the current study, and while the current design does not deter from the possibility of re-test effects, the evidence suggests that the interventions are effective in improving cognitive or motor functioning, which may be applied when interpreting the current study findings. Additionally, an analysis to control for regression to the mean, which included baseline cognitive DTC performance as a covariate, showed similar results as our *post-hoc* analysis comparing low versus high MoCA scorers, such that there was greater improvement in cognitive DTCs in the participants with low baseline MoCA performance compared to high baseline MoCA performance. This finding suggests that our results remain significant even after controlling for regression to the mean.

Another important note to consider is that characteristics such as age and baseline neuropsychological performance may impact practice effects, with researchers showing that there are smaller practice effects in older adults compared to younger adults, as well as older adults who have poorer memory performance (Calamia et al., 2012). Given that the dual-task facilitation effect following training was primarily driven by older adults with low MoCA scores, we believe that more than 12 weeks between the pre-and post-training assessments was sufficient to reduce practice effects in this population. Nevertheless, without a control group, it is not possible to conclude whether the improvements in dual-task cognitive accuracy were not due to re-test effects, so the results should be interpreted with this in mind.

Comparable improvement in dual-task performance across training modalities

The finding that cognitive DTCs improved regardless of training modality is consistent with our second hypothesis. While our small sample size may have left the interaction analyses underpowered, we included effect sizes to aid in interpreting our results. The effect sizes suggest similar improvement across training modalities, with the executive function training having a large effect size, and the aerobic exercise and gross motor training having moderate effect sizes. Analyses including baseline cognitive DTC scores as a covariate showed similar findings of null group differences, suggesting that the level of improvements observed across each training group was not solely due to a regression to the mean. Moreover, in a joint study involving the same training design and participants as the current study, but with a larger sample size (i.e., n = 78; Pothier et al., 2021), results show similar improvements in TUG walking speed regardless of training

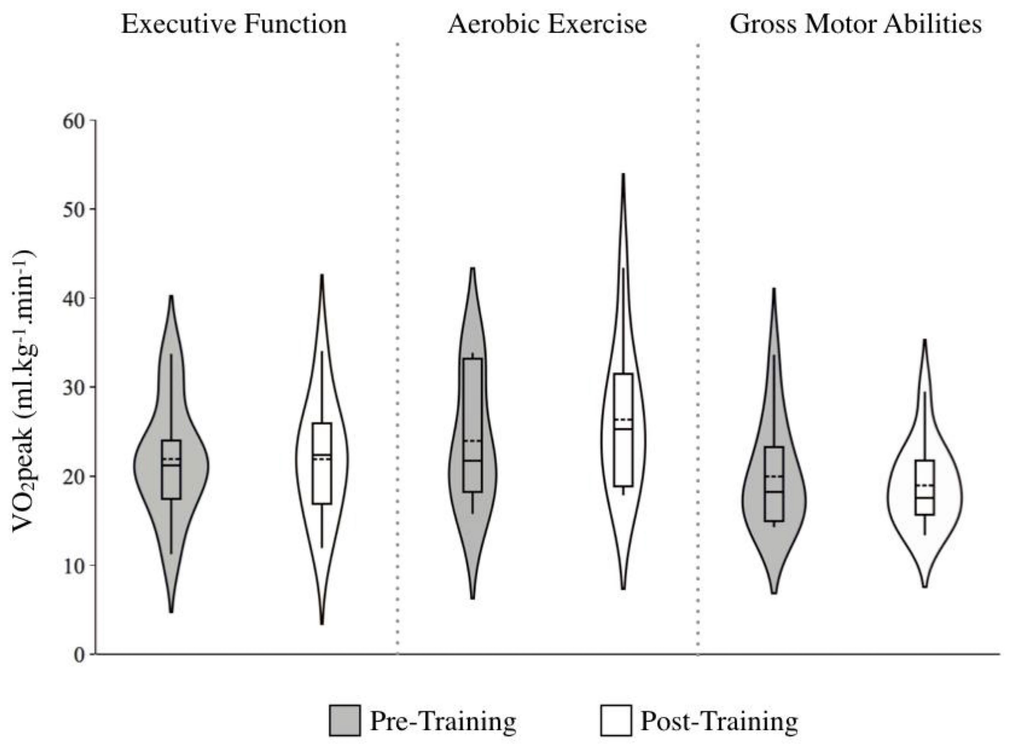

FIGURE 6
Marker of cardiorespiratory fitness (i.e., VO2peak) before and after training across training groups. Note. Higher scores indicate better cardiorespiratory fitness. The length of each curve represents the range of scores, the width represents the frequency of data points in each region, the solid line within each boxplot represents the median, and the dotted line represent the mean. While VO_{2peak} improved following aerobic exercise training (g =0.31 [small effect] Δ=9.07%), the interaction effect only approached significant. As the aerobic exercise group had the highest VO_{2peak} levels at baseline, this may have limited the possibility for further improvement through training.

modality. We found consistent results in TUG improvements in the current sub-sample of 33 participants, suggesting that the training effects are representative of the full dataset. As such, while the small sample size is an important limitation to consider, we provide moderate evidence that may suggest similar improvements in cognitive DTCs across training modalities.

Importantly, our findings are consistent with a number of other studies which have revealed comparable improvements in dual-task walking speed and balancing (Desjardins-Crepeau et al., 2016; Fraser et al., 2017), as well as functional mobility (Pothier et al., 2021) following different combinations of cognitive and aerobic exercise training. Our findings are also in line with research demonstrating similar improvements in single- and dual-task cognitive performance following either combined high-intensity aerobic and strength training or gross motor activities (Berryman et al., 2014).

Together, our research contributes to the growing view that multiple types of interventions may be beneficial for maintaining cognitive and motor functioning in older adults. Future preference clinical trial designs may test whether having the option to participate in either cognitive or physical training might promote sustained adherence to training or could lead to increased self-efficacy in the context of cognitive-motor dual-task outcomes.

Mechanisms underlying dual-task improvements

Given the apparent multiple routes perspective, our final aim was to better understand *how* these various interventions lead to similar improvements in dual-task performance. Executive function performance was only found to improve following the cognitive intervention, as demonstrated by reduced response times on the Stroop inhibition and switching conditions. By increasing cognitive capacity, additional resources may have been allocated to the cognitive task while dual-tasking, thereby improving performance (Li et al., 2018). Additionally, the energy demands associated with walking were found to specifically improve following gross motor activities. By increasing gait coordination and subsequently reducing the amount of energy needed to walk, dual-tasking may have been less demanding as it would require fewer physical and cognitive resources (Van Swearingen and Studenski, 2014). Finally, we hypothesized that cardiorespiratory fitness would improve the most following aerobic exercise; however, the effect size to support this was small. While the statistical testing approached significance, our results showed a 9% increase in cardiorespiratory fitness

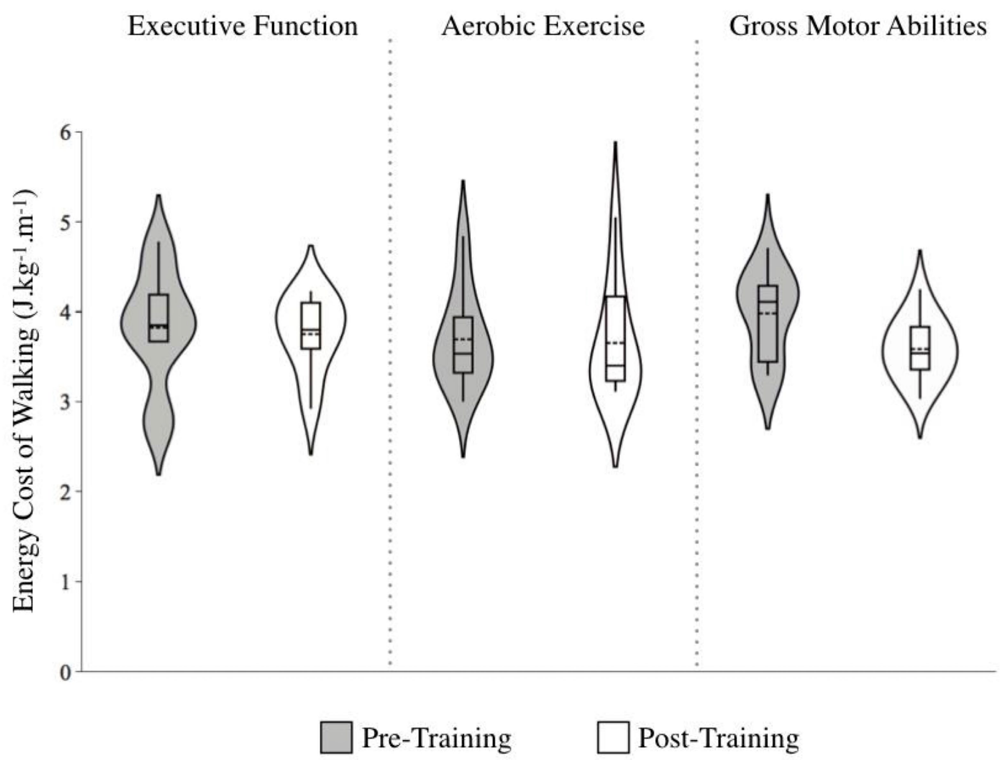

FIGURE 7
Energy cost of walking (ECW) before and after training across training groups. Note. Lower scores indicate more efficient walking. The length of each curve represents the range of scores, the width represents the frequency of data points in each region, the solid line within each boxplot represents the median, and the dotted line represent the mean. Improvements in ECW were found following gross motor abilities training (g =−0.94 [large effect] Δ=−11.0%), although the interaction effect was not significant.

following aerobic exercise, which points to an important distinction between statistical and clinical significance. Indeed, Hawkins and Wiswell (2003) report that in older adults, VO_{2max} declines 10% per decade. Therefore, our results are clinically significant as they suggest that a relatively short-term intervention can counteract the age-normative decline in cardiorespiratory fitness. Moreover, one reason we may not have observed a statistically significant effect is due to the high baseline cardiorespiratory fitness found in the AE group, which may have limited the possibility for further improvement through training. Based upon the findings from Pothier et al. (2021), which utilized the same population and training design, but had a larger sample size, significant improvements in cardiorespiratory fitness were observed following aerobic exercise training. This therefore points to the potential limitation of our sample which had higher baseline VO_{2peak} values.

Conclusion

The present research elucidates the impact of cognitive or physical training on the separate cognitive and motor components involved in dual-tasking and considers how different interventions may work towards improving dual-task behavior. The results suggest that regardless of training modality (EF, AE, GMA), older adults improved their cognitive performance during dual-task walking, while maintaining their gait speed. This contributes to the growing body of literature which provide evidence for a multiple routes perspective (i.e., Berryman et al., 2014; Desjardins-Crepeau et al., 2016; Fraser et al, 2017; Pothier et al., 2021). Specifically, this perspective argues that while different forms of cognitive and physical training lead to similar improvements in cognitive or motor performance, they do so through varying mechanisms. For instance, improvements in dual-task performance may have resulted from increasing executive functions following cognitive training, enhancing cardiorespiratory fitness following aerobic exercise, and reducing the metabolic energy demands following gross motor coordination training. Also notable from this research is the cognitive dual-task facilitation that was observed post-training, particularly for older adults with lower baseline cognitive status. This highlights the potential for cognitive enhancement to alter attentional allocation under complex walking conditions in individuals with lower cognitive ability. Our research findings are important given the functional implications of reduced dual-task performance in old age (e.g., increased risk of falls, cognitive impairment). However, due to the limitations of this study, including a small sample size and lack of a control group, future research is needed to substantiate the current study findings, ideally in a larger randomized control trial.

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 Institut Universitaire Gériatrie de Montreal ethical research committee and Concordia University's Human Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

RD: conceptualization, data curation, methodology, validation, formal analysis, and writing—original draft—reviewing and editing. LBh: conceptualization, data curation, funding acquisition, investigation, methodology, project administration, validation, and Writing—reviewing and editing. KP: conceptualization, data curation, methodology, project administration, validation, and writing—reviewing and editing. TVr: conceptualization, data curation, formal analysis, methodology, validation, and writing—reviewing and editing. BI: conceptualization, data curation, methodology, project administration, validation, and writing—reviewing. NB: conceptualization, data curation, funding acquisition, methodology, validation, and writing—reviewing and editing. ML: conceptualization, data curation, formal analysis, methodology, validation, and writing—reviewing. TVi: data curation, methodology, project administration, validation, and writing—reviewing. AK: conceptualization, funding acquisition, validation, and writing—reviewing and editing. AN: conceptualization, data curation, funding acquisition, investigation, validation, and writing—reviewing. TVu: conceptualization, data curation, funding acquisition, investigation, validation, and writing—reviewing. LBo: conceptualization, funding acquisition, validation, and writing—reviewing. KL: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, validation, and writing—reviewing and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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