IMPLICATIONS FOR LIFESTYLE BEHAVIORS IN COGNITIVE FUNCTION

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IMPLICATIONS FOR LIFESTYLE BEHAVIORS IN COGNITIVE FUNCTION

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Effect of Acute Moderate-Intensity Exercise on the Mirror Neuron System: Role of Cardiovascular Fitness Level

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Objectives: The aims of this study were to use functional near-infrared spectroscopy (fNIRS) to determine whether cardiovascular fitness levels modulate the activation of the mirror neuron system (MNS) under table-setting tasks in non-exercise situation, to replicate the study that positive effect of acute moderate-intensity exercise on the MNS and investigate whether cardiovascular fitness levels modulates the effect of exercise on the activation of the MNS.

Methods: Thirty-six healthy college-aged participants completed a maximal graded exercise test (GXT) and were categorized as high, moderate, or low cardiovascular fitness. Participants then performed table-setting tasks including an action execution task (EXEC) and action observation task (OBS) prior to (PRE) and after (POST) either a rest condition (CTRL) or a cycling exercise condition (EXP). The EXP condition consisted of a 5-min warm-up, 15-min moderate-intensity exercise (65% VO_{2max}), and 5-min cool-down.

Results: No significant differences were observed for Oxy-Hb and Deoxy-Hb between different cardiovascular fitness levels in the EXEC or OBS tasks in the non-exercise session. But there were significant improvements of oxygenated hemoglobin (Oxy-Hb) in the inferior frontal gyrus (IFG) and pre-motor area (PMC) regions under the OBS task following the acute moderate exercise. Particularly, the improvements (Post-Pre) of Δ Oxy-Hb were mainly observed in high and low fitness individuals. There was also a significant improvement of deoxygenated hemoglobin (Deoxy-Hb) in the IPL region under the OBS task. The following analysis indicated that exercise improved Δ Deoxy-Hb in high fitness individuals.

Conclusion: This study indicated that the activation of MNS was not modulated by the cardiovascular fitness levels in the non-exercise situation. We replicated the previous study that moderate exercise improved activation of MNS; we also provided the first empirical evidence that moderate-intensity exercise positively affects the MNS activation in college students of high and low cardiovascular fitness levels.

Keywords: mirror neuron system, action understanding, social cognition, cardiovascular fitness level, acute moderate-intensity exercise, fNIRS

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INTRODUCTION

Mirror neuron system (MNS) was activated when an individual performed action, and observed the same action performed by others (Sun et al., 2018). The first discovery of MNS was in the ventral premotor cortex (area F5) of the macaque brain; it fired when grasping food as well as when the macaque observed the experimenter grasping food. Then, the MNS was found in the rostral inferior parietal lobule (IPL) (PF/PFG), also firing when a monkey executes a goal-related action and mouth actions, as well as observing the same action in another subject (Rizzolatti et al., 1996; Gallese et al., 2004; Fogassi et al., 2005). Previous work has determined the location of the MNS in the human (Buccino et al., 2001; Gallese et al., 2004; Filimon et al., 2007; Kilner et al., 2009; Molenberghs et al., 2010) and its functions for action understanding (Johnson-Frey et al., 2003; Leslie et al., 2004) and imitation (Buccino et al., 2004; Bernier et al., 2013). A more general hypothesis was that the MNS also played a crucial role in social cognition to catch the intentions and emotions of others (Gallese, 2006; Pfeifer et al., 2008; Perkins et al., 2010). Then Language evolved became a powerful and flexible tool when humans developed a social function to exchange knowledge (Tomasello et al., 2005). However, several studies were skeptical about the role that the MNS played in social cognition, arguing that the MNS was simply the motor controller and did not include action understanding which is one of the most important basic functions in social cognition (Baird et al., 2011; Hickok et al., 2011b). Besides, other studies declared that the dorsal part of the premotor cortex in MNS did play a role in action understanding, but only the dorsomedial prefrontal of MNS which was called the mentalizing system (MENT) activated by the social relevant tasks (Spunt and Lieberman, 2012; Geiger et al., 2019).

In the field of sport psychology, cardiovascular fitness level was considered as one of the most important factors. Several studies have indicated that high fitness was associated with greater brain volume and functional connectivity (Chaddock et al., 2010; Voss et al., 2010). The role of fitness in the cognitive performance was also investigated in prior studies. Åberg et al. (2009) have shown that young adulthood with higher fitness levels would perform better in cognitive tasks. And one study researched on 877 older adults indicated that higher fitness level was associated with better motor skills, cognitive performance, and memory (Freudenberger et al., 2016). Although several studies revealed higher fitness levels related to better daily performances, there is still no study to reveal the relationship between cardiovascular fitness levels and the activation of MNS in the action understanding tasks which might be the basic neural mechanism to social function, language function, and cognitive function.

Exercise has also been shown to benefit cognition (Audiffren et al., 2009; Byun et al., 2014), the hippocampus and memory (Sayal, 2015), and improved motor control in early Parkinson's disease patients (Fisher et al., 2008), social behaviors in children with autism (Bremer et al., 2016), as well as adolescents with attention-deficit/hyperactivity disorder (ADHD) (Kamp et al., 2014). Previous work done by Drollette et al. (2012) has shown that preadolescent children had a greater performance on the cognitive control task (Flanker task) after 15 min of moderate-intensity running at 60% maximal heart rate (HR_{max}) compared with resting state. Furthermore, a recent study used functional near-infrared spectroscopy (fNIRS) also demonstrated that moderate-intensity exercise could improve the activation of MNS in an action understanding social task (Xu et al., 2019), which indirectly outlined one of the neural bases of exercise improved social behaviors in children with autism. Although Xu et al. (2019) have shown the positive effect of exercise on the MNS, more studies are still needed to verify this effect.

With in-depth study, some previous studies have observed different effects of exercise on cognitive performance among different cardiovascular fitness levels. For example, Chu et al. (2015) found that acute moderate-intensity exercise can improve the performance of cognitive functions and to a specific improvement in the executive function of high and low cardiovascular fitness levels in older adults. Chang et al. (2012) also indicated the improvement of cognitive performances which are the information processing, attention, and executive function tasks after a delay of light and moderate-intensity exercise on high and low-fit younger adults in their meta-analysis study. Previous reviews also highly recommended cardiovascular fitness should be measured and analyzed in the study (Brisswalter et al., 2002; Tomporowski, 2003). Those studies mentioned above indicated that cardiovascular fitness might modulate the effect of exercise on cognitive functions, since the function of MNS was relevant with cognitive control, for example, patients with impairment of motor control and aphasia (mouth action control) after stroke were also following less activation of MNS (Small et al., 2012). However, how cardiovascular fitness level modulates the effects of acute exercise on the MNS in action understanding tasks remains less understood and warrants more explorations.

Therefore, the aims of this study were to determine whether MNS activation is related to the cardiovascular fitness level in the non-exercise situation, to replicate a study done by Xu et al. (2019), that is acute exercise can improve MNS response in the action understanding tasks and to evaluate whether the effect of moderate-intensity exercise on MNS is modulated by cardiovascular fitness, Specifically, we also made the following hypotheses.

Hypothesis 1: Because prior studies illustrated that higher cardiovascular fitness level was related to better cognitive performance (Freudenberger et al., 2016), the MNS regions with high fitness individuals should exhibit the largest activation compare with moderate and low fitness groups in non-exercise session under our action understanding tasks.

Hypothesis 2: Because the previous study has shown moderate-intensity exercise increased activation of MNS in the OBS task (Xu et al., 2019), thus, parts of MNS regions activation will be increased after exercise in the OBS task.

Hypothesis 3: Because plenty of evidence indicated that the effect of exercise mainly benefits high-and low-fit individuals' cognitive performances (Chang et al., 2012), the subgroup-analyses will show the improvements of MNS in cardiovascular high and low fitness level individuals following exercise under action understanding tasks.

MATERIALS AND METHODS

Participants

Thirty-six college-aged participants were recruited to this study (mean age 20.6 ± 1.5 years, height 169 ± 9 cm, body, weight 61.4 ± 12.5 kg; 16 females). All participants were healthy and right-handed (Edinburgh Handedness Inventory score > 0.85), and all had a normal or corrected-to-normal vision. All participants completed four sessions (body test, experimental, control, and acute exercise sessions) and were instructed to avoid any intense exercise in 24 h between each session. All participants completed a maximal oxygen consumption test and were then split into three groups based on the American College of Sports Medicine (ACSM) guidelines (American College of Sports Medicine [ACSM], 2013). The maximal oxygen consumption (VO_{2max}) of each fitness group was categorized as: low fitness group, moderate fitness group, and high fitness group (**Table 1**). According to ACSM guidelines, these groups have previously been described as having poor (35.4–43.5 ml/kg/min for male; 26.2–33.6 ml/kg/min for female), fair (43.5–49.1 ml/kg/min for male; 33.6–38.9 ml/kg/min for female), and good fitness (49.1 above ml/kg/min for male; 38.9 above ml/kg/min for female), respectively (American College of Sports Medicine [ACSM], 2013). Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of Guangzhou Sport University.

Experimental Procedures

In the first session, participants were fully informed regarding each experimental session. Each participant gave written informed consent and filled out an International Physical Activity Questionnaire (IPAQ). Participants meeting the inclusion criteria then performed a test of cardiovascular fitness to VO_{2max} and were categorized into high, moderate, and low fitness group according to the ACSM guidelines (American College of Sports Medicine [ACSM], 2013).

The second and third sessions were the table-setting task, which has both action execution (EXEC) and action observations (OBS) tasks under experimental (EXP) and control (CTRL) conditions. By definition, acute exercise session occurred only in the EXP condition. During the acute exercise session, all participants performed 25 min of exercise on a cycle ergometer (Ergoselect 100, ergoline GmbH, Germany) that consisted of a 5 min warm-up, 15 min of exercise at moderate intensity (65% HR_{max}), and a 5 min recovery period. Heart rate (HR) was monitored by a wireless HR monitor (Acentas pulse meter, BM-CS5EU, Beijing, China). The initial cycling workload was 30 W and automatically increased in the warm-up period until HR reached 65% $HR_{max.}$ The cycle ergometer system automatically adjusts the workload if the HR is higher than target HR to ensure they were exercising at moderate intensity over the 15-min exercise period. Finally, participants were allowed to cool down during the recovery period at 30 W. Under the CTRL condition, participants conducted the same action execution and observation components, but rested instead of performing the exercise (**Figure 1A**).

All participants performed the table-setting task before (PRE) and after (POST) the acute exercise session or rest in the EXP and CTRL conditions. If participants individually attended exercise sessions of the experiment firstly, they performed another session on different days.

Maximal Oxygen Consumption Test

All participants had their body mass index (BMI) measured in the laboratory. The IPAQ was used to assess participants' physical activity. Cardiovascular fitness was measured using cardiopulmonary exercise testing (Jaeger-Masterscreen-CPX, Carefusion, Germany). All participants ran on a treadmill (h/p/cosmos airwalk, Germany) using the Bruce protocol for the maximal graded exercise test (GXT) (Bruce et al., 1973). VO_{2max} was determined if participants met at least three of the following four criteria: (1) respiratory exchange rate (RER) ≥ 1.15; (2) volitional exhaustion; (3) no increase in HR with increasing intensity; (4) rating of perceived exertion (RPE) ≥ 17 (Borg, 1982; Seifert et al., 2010). Participants were asked to rate their exertion on the RPE scale in the last 20 s of the GXT intensity stage before increasing workload.

The Table-Setting Task to Reflect the MNS Activity

In the initial period, participants and the experimenter (the experimenter is male in this study) sat face to face. The storage box was placed in front of the participant and the placemat placed on their right-hand side. The storage box included five table items: a plate, a saucer, a pair of chopsticks, a soupspoon, and a rice bowl. A monitor placed at a 45° angle in front of participants to presented visual cues.

In the executive (EXEC) task of the experiment, the participants were instructed to place the table items orderly onto and round the placemat with a normal, natural speed, and rhythm in 15 s after the cue was on the monitor: a picture of a cup. Participants were instructed to only use their right-hand and avoid any other movements. Then, their eyes continued to focus on the monitor that displays a cross to remind participants to remain still and avoid any movements for 20 s; this is block 1. In block 2, the four table items will be restored and placed into the storage box, with the bowl placed in front of the box in the identical order in 15 s, then with 20 s to rest. There were eight blocks in this task, block 3 and 4, block 5 and 6, block 7 and 8 were the same as block 1 and 2. The order of placement was always fixed: plate, saucer, chopsticks, soup spoon, and rice bowl (**Figure 1B**).

In the observation (OBS) task of the experiment, the table items, storage box, and placemat were turned toward to the experimenter. The visual procedures were the same as the EXEC

TABLE 1 | Participants' demographic and physiological characteristics for low, middle, and high fitness groups (mean ± SD).

Variable	High fitness	Moderate fitness	Low fitness	Total
Sample size	12	13	11	36
Gender (male)	8	7	5	20
Age (yr)	20.44 ± 1.62	20.93 ± 1.49	20.27 ± 1.27	20.58 ± 1.48
Height (cm)	171.05 ± 6.38	168.87 ± 9.54	167.64 ± 10.54	168.53 ± 8.70
Weight (kg)	62.59 ± 9.81	63.71 ± 11.92	60.06 ± 15.624	61.44 ± 12.53
BMI (kg.m^{-2})	21.27 ± 2.09	22.19 ± 2.80	21.07 ± 3.48	21.45 ± 2.92
IPAQ (METs/wk)	3342 ± 1726	3909 ± 2501	2125 ± 1286	2960 ± 1863
VO_{2max} (mL.kg^{-1}.min^{-1}) for women	41.78 ± 1.68^a	36.83 ± 0.69^b	32.37 ± 1.65^c	36.43 ± 3.94
VO_{2max} (mL.kg^{-1}.min^{-1}) for men	55.74 ± 3.02^a	48.01 ± 1.26^b	41.56 ± 2.72^c	49.49 ± 6.26
VO_{2max} (mL.kg^{-1}.min^{-1}) for men and women	51.08 ± 1.80^a	42.85 ± 1.74^b	36.60 ± 1.88^c	43.69 ± 8.44

BMI, body mass index; IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent; means with different superscripts a, b, and c are significantly different from one another.

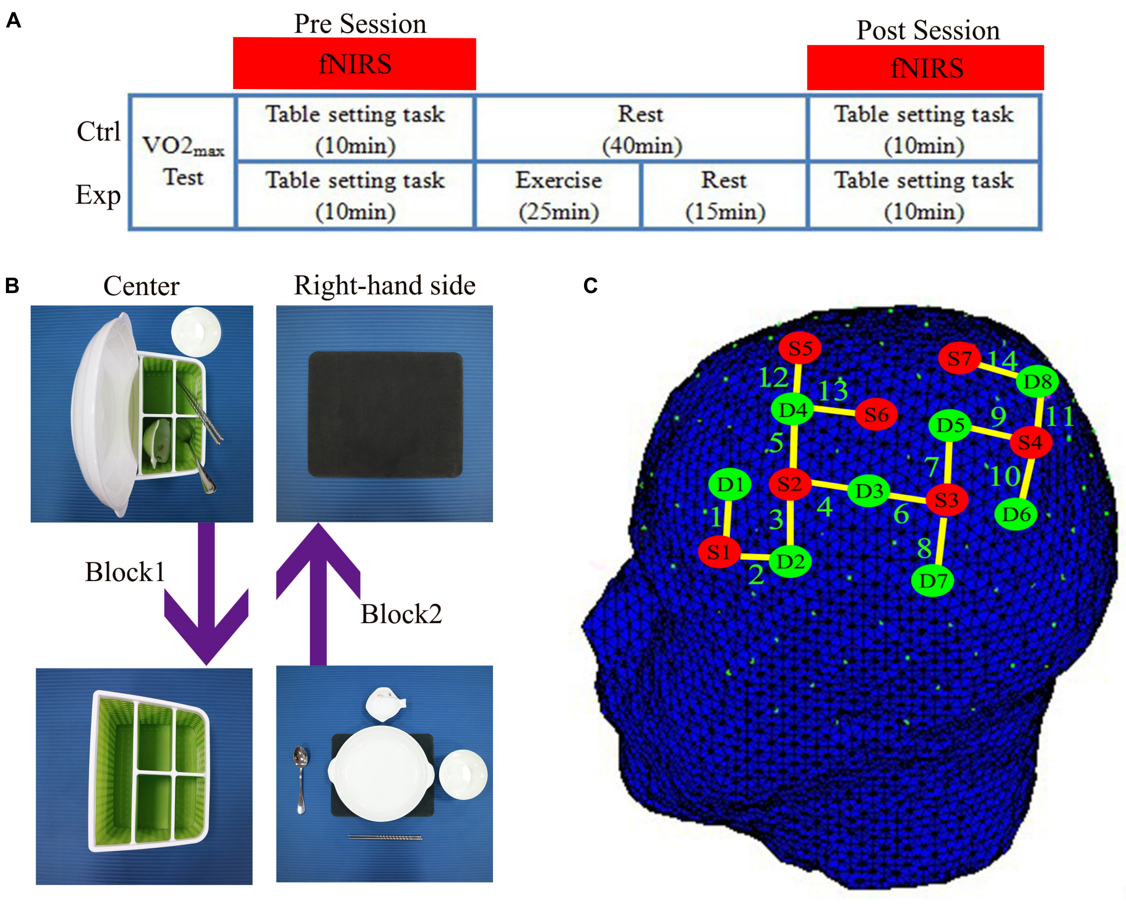

FIGURE 1 | (A) The experimental design showed the experimental (Exp) condition and the control (Ctrl) condition. Using functional near-infrared spectroscopy (fNIRS) to measure cortical hemodynamic changes while subjects performed the table-setting tasks before (Pre) and after (Post) exercise or rest. **(B)** Illustration of the design of the table-setting tasks. **(C)** fNIRS optode placement according to the 10–10 International System. Red dots represent the position of light sources. Green dots represent the position of detectors. Yellow lines depict channels.

task. The experimenter moved the table items, and participants carefully observed the movements. When the experimenter rested and watched the cross on the monitor, participants also focused on the cross and avoided any movements during the whole OBS task.

fNIRS Data Acquisition

fNIRS data were acquired using the NIRSport system (NIRx Medical Technologies, LLC, Glen Head, NY, United States). Probe-channel sets were installed with reference to the international 10/10 system into a NIRS-EEG compatible cap (EASYCAP, Herrsching, Germany) and then placed on the participant's head. The cap position was centered at the Cz point, and then thin plastic straps were inserted between probes to ensure that the distance was less than 3 cm between each source and detector. The fNIRS system consisted of eight light sources and eight detectors which formed 14 channels covering most of the MNS region on the participant's left hemisphere. Channels 1, 2, and 3 consisted of IFG (BA44/45), channels 4, 5, 12, and 13 consisted of PMC (BA6), channels 6, 7, and 8 consisted of rostral IPL (BA40), and channels 9, 10, 11, and 14 consisted of SPL (BA7) (**Figure 1C**). An already existing NIRS 10 × 10 positions were used to estimate the NMI coordinates of optodes with respect to the EEG 10/5 positions. The locations of NIRS channels were defined using the maximum probability method (**Table 2**). The ROIs were determined while three or four channels covered one Brodmann Area. We placed channels only in the left hemisphere because the left hemisphere is dominant when subjects perform a right-handed action (Filimon et al., 2007; Egetemeir et al., 2011). Prior to recording, the NIRStar acquisition software (NIRx Medical Technologies, LLC, Glen Head, NY, United States) recorded fNIRS data and verified the signal quality according to the NIRStar manual. The baseline was set while each participant was resting for 15 s prior to the table-setting test to remove irrelevant noise and signal drift (Fu et al., 2016).

Data Preprocessing

Raw data from each participant were processed within the nirsLAB analysis package (v2017.06, NIRx Medical Technologies, LLC, Los Angeles, CA, United States). Discontinuities were automatically corrected or deleted by the nirsLAB (std threshold = 5). Spikes were interpolated or manually deleted. A bandpass filter was used; 0.01 Hz was used to remove drift and 0.1 Hz was used to filter respiratory noise. We used the modified Beer–Lambert law (Cope et al., 1988) to analyze the optical data from the fNIRS system. The changes in oxygenated hemoglobin (Oxy-Hb), deoxygenated hemoglobin (Deoxy-Hb), and total hemoglobin (Total-Hb) concentration data were collected at a sampling rate set at 7.81 Hz.

Statistical Analyses

All descriptive characteristics (age, height, weight, BMI, IPAQ, and VO_{2max}) were imported into IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, United States), and then a one-way ANOVA was used to compared characteristics between cardiovascular fitness levels (high, moderate, and low).

The statistical parametric mapping (SPM) level 1 (within-subject) package incorporated into nirsLAB was based on the canonical hemodynamic function (parameters in nirsLAB = [6 16 1 1 6 0 32]) to determine event-related changes in Oxy-Hb, Deoxy-Hb, and total-Hb during action execution and observation. Finally, the *beta* values of the Oxy-Hb and Deoxy-Hb were exported from each participant for statistical analysis. Second-level analyses (SPM 2) level 2 assessed differences in groups to export brain activation maps.

The *beta* values of the Oxy-Hb and Deoxy-Hb from each ROI of the participant as the dependent variable were imported to IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, United States). The one-way ANOVA was applied to compare Oxy-Hb and Deoxy-Hb between levels in non-exercise session (CTRL PRE, CTRL POST, and EXP PRE sessions). Then Oxy-Hb and Deoxy-Hb were subjected to three-way repeated measure ANOVA under different tasks (EXEC and OBS) with three factors: conditions (EXP and CTRL), time sessions (PRE and POST) as within-subject factors, cardiovascular fitness levels (high, moderate, and low) as a between-subject factor. Then when it exhibited main effect on conditions and three-way interaction was significantly different, following two-way repeated measure ANOVA used Bonferroni correction method was applied to the [Post–Pre] Oxy-Hb or Deoxy-Hb contrast (Δ Oxy-Hb and Δ Deoxy-Hb) of EXP and CTRL conditions in these ROIs to compare the effect of exercise on the MNS-related regions that were known as activated by action execution and action observation. We used contrast value of Oxy-Hb or Deoxy-Hb because it would help to eliminate potential variations as different MNS activation may be caused by doing the tasks on different days. All values are presented as mean ± SE. An alpha of 0.05 was used as the statistical significance level for all comparisons.

RESULTS

Participant Characteristics

We summarize the basic descriptive characteristics for the three-fitness level. One-way ANOVA indicated no significant difference among fitness levels on the demographic variables of age, height, weight, BMI, and IPAQ. As expected, VO_{2max} was significantly different between fitness levels [$F(2, 33) = 15.73$, $P < 0.001$], and *post hoc* analyses revealed that all three groups were significantly different from each other. The high fitness level group showed the highest VO_{2max} value, the moderate fitness group followed, and the low fitness group had the lowest value (**Table 1**).

Cortical Hemodynamic Change in OBS Task

In the OBS task, the one-way ANOVA was conducted on each ROI to determine whether the Oxy-Hb and Deoxy-Hb were significant differences between levels in non-exercise session (CTRL PRE, CTRL POST, and EXP PRE sessions). However, it revealed no significant differences between cardiovascular fitness levels with regard to Oxy-Hb and Deoxy-Hb.

The three-way repeated measures ANOVA was performed on each of the ROI of the Oxy-Hb and Deoxy-Hb. It revealed a significant main effect on conditions [$F(2,33) = 9.30$, $P < 0.05$, $\eta^2 = 0.22$], a significant interaction between conditions, time sessions, and cardiovascular fitness levels [$F(2,33) = 3.42$, $P < 0.05$, $\eta^2 = 0.17$] in IFG region. It also revealed a significant main effect on conditions [$F(2,33) = 4.70$, $P < 0.05$, $\eta^2 = 0.13$] and a marginal significant interaction [$F(2,33) = 2.70$, $P = 0.08$, $\eta^2 = 0.14$] in the PMC region. However, there was

TABLE 2 | The MNI coordinate of each channel, the source, and detector positions are in the 10-10 system.

Channel	Source—Detector	MNI coordinate X	Y	Z	Brodmann area and anatomical label (percentage overlap)
1	F5–F3	−46	39	26	45—Pars triangularis Broca's area (72.56%)
2	F5–FC5	−56	24	20	45—Pars triangularis Broca's area (53.08%)
3	FC3–FC5	−55	12	34	44—Pars opercularis, part of Broca's area (47.81%)
4	FC3–C3	−50	−3	50	6—Pre-motor and supplementary motor cortex (61.71%)
5	FC3–FC1	−38	12	55	6—Pre-motor and supplementary motor cortex (37.52%)
6	CP3–C3	−52	−34	52	40—Supramarginal gyrus part of Wernicke's area (43.32%)
7	CP3–CP1	−39	−48	60	40—Supramarginal gyrus part of Wernicke's area (41.82%)
8	CP3–CP5	−57	−48	38	40—Supramarginal gyrus part of Wernicke's area (65.46%)
9	P1–CP1	−24	−62	62	7—Somatosensory association cortex (82.72%)
10	P1–P3	−32	−73	47	7—Somatosensory association cortex (69.67%)
11	P1–PZ	−13	−73	56	7—Somatosensory association cortex (91.59%)
12	FCZ–FC1	−13	12	67	6—Pre-motor and supplementary motor cortex (73.21%)
13	C1–FC1	−26	−5	68	6—Pre-motor and supplementary motor cortex (81.78%)
14	CPZ–PZ	2	−61	66	7—Somatosensory association cortex (58.83%)

The Brodmann area with maximum probability was used in final location of each channel.

no significant interaction in the IPL and SPL regions. In order to determine which fitness level of activation of these two ROIs were increased by exercise, two-way repeated measure ANOVA was used to compare the contrast value (Δ Oxy-Hb) of EXP and CTRL conditions. It indicated that was a significant difference in the low fitness level [$F(2,33) = 5.11$, $P < 0.05$, $\eta^2 = 0.13$, Bonferroni-corrected] in IFG region. Also, it exhibited significant difference in the high fitness level [$F(2,33) = 17.36$, $P < 0.001$, $\eta^2 = 0.35$, Bonferroni-corrected] and low fitness level [$F(2,33) = 7.62$, $P < 0.05$, $\eta^2 = 0.19$, Bonferroni-corrected] in the PMC region. However, there was no significant difference in PMC and IFG regions in the moderate fitness level (**Figure 2**).

With regard to Deoxy-Hb, there was a significant main effect in conditions [$F(2,33) = 7.92$, $P < 0.05$, $\eta^2 = 0.19$], a significant interaction between conditions, time sessions, and cardiovascular fitness levels [$F(2,33) = 3.33$, $P < 0.05$, $\eta^2 = 0.17$] in IPL region. In order to determine which fitness level of activation of this ROI was increased by exercise, two-way repeated measure ANOVA was used to compare the contrast value (Δ Deoxy-Hb) of EXP and CTRL conditions. It indicated that was a significant difference in the high fitness level [$F(2,33) = 6.14$, $P < 0.05$, $\eta^2 = 0.16$, Bonferroni-corrected] in IPL region. There was no significant difference in the IPL region in the moderate and low fitness levels.

Cortical Hemodynamic Change in EXEC Task

In the EXEC condition, the one-way ANOVA was also conducted to each ROI determine whether the Oxy-Hb and Deoxy-Hb were significantly different between levels of fitness in the non-exercise session, which were not affected by exercise. The results revealed no significant differences between cardiovascular fitness levels for Oxy-Hb and Deoxy-Hb.

The three-way repeated measures ANOVA was also performed on each of the ROI of Oxy-Hb and Deoxy-Hb, it revealed no significant main effect on conditions or interaction between conditions, time sessions, and cardiovascular fitness levels for both Oxy-Hb and Deoxy-Hb. The data that support the findings of this study are openly available in Mendeley at http://dx.doi.org/10.17632/s8tp7d75dw.1.

DISCUSSION

Our study indicated that there was no significant difference between fitness levels with EXEC or OBS task under non-exercise session, which implied different cardiovascular fitness levels could not reflect different activation of MNS under this table-setting social task and denied Hypothesis 1. Wright et al. (2019) evidenced that physical development is positively correlated with cognitive performance, language ability, and social-emotional state. Higher fitness level has been shown that was associated with better average accuracy and response time across all level of spatial memory tasks, lower switch cost in elderly adults, these higher fitness older adults also showed a greater functional connectivity which was related to better cognitive function (Voss et al., 2010; Prakash et al., 2011). Some investigations have shown that physical fitness level was relevant to language development. One study indicated that compared with typical developmental children, children with developmental language disorders showed worse performance on vertical jump (Muursepp et al., 2014). Also, the physical fitness performance of children with developmental language disorders was significantly lower than those of typical children (van der Niet et al., 2014). Although our study showed that there was no significant difference between cardiovascular fitness levels and MNS activation, it does not conflict with previous works because the cognitive function, social cognition, and language function are still different functions in the human brain, and participants were both college students which generally excluded language developmental disorders. And the most crucial point is that the values of VO_{2max} in the low level of our participants were also higher than those with language developmental disorders

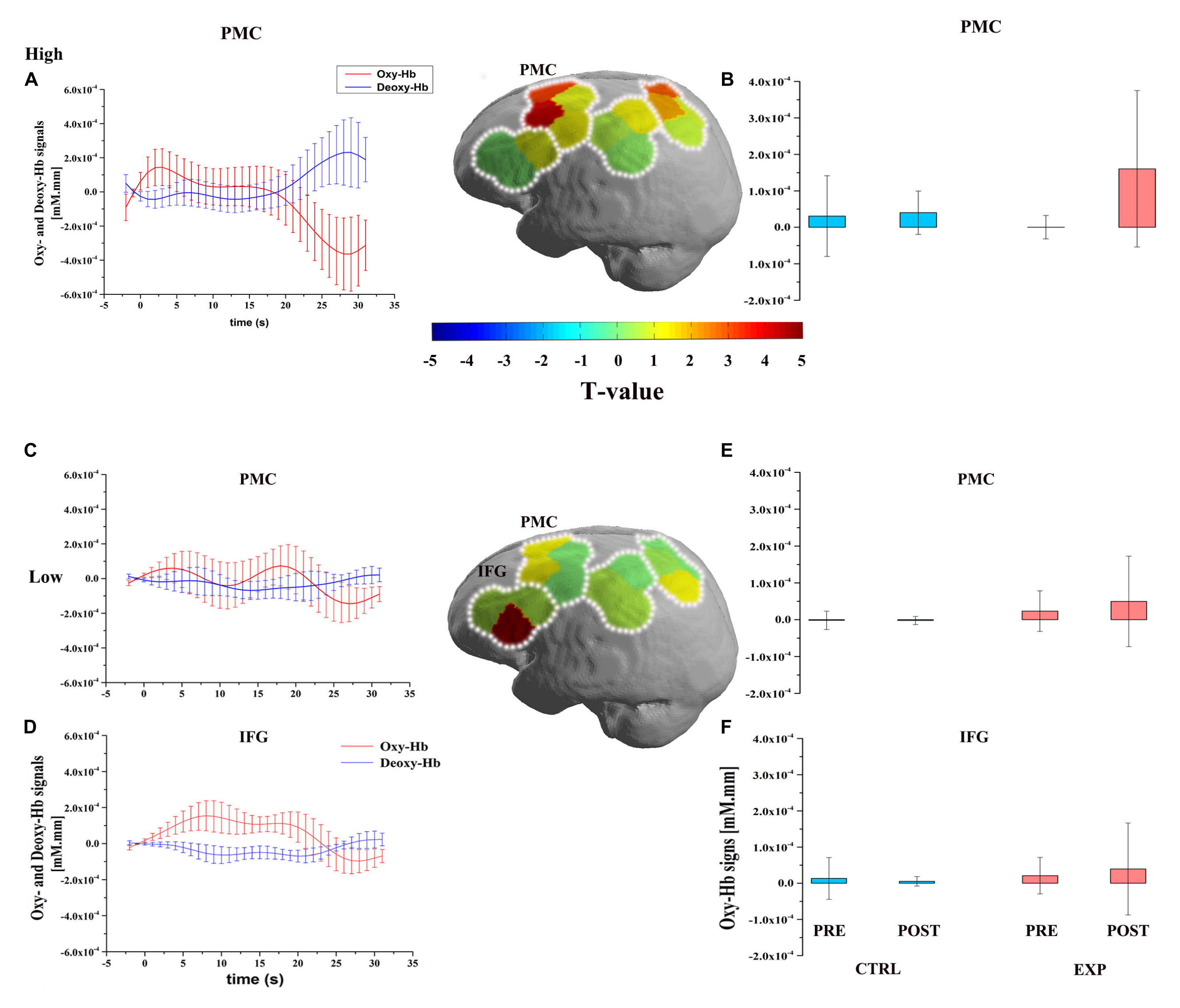

FIGURE 2 | Figures describe the significant improvement of oxygenated hemoglobin Δ Oxy-Hb response after exercise during the OBS task. The upper part is the cortical activation patterns with high cardiovascular fitness level (high: **A,B**) and the lower part is the cortical activation patterns with low cardiovascular fitness level (low: **C–F**). Three graphs of first column depict the timelines for the significant Δ Oxy-Hb (red) and Δ Deoxy-Hb (blue) signal which are shown in arbitrary units (mM·mm) **(A,C,D)**. Significant Oxy-Hb signal changes in ROIs during the OBS task in all conditions are shown in the last column. Error bars indicate standard error **(B,E,F)**. Middle figures are t-map of oxy-Hb signal contrast activation in the OBS task. T-values are shown according to the color bar.

relatively. More studies are needed to determine whether cardiovascular fitness level reflects social and language cognition.

Mirror neuron system has been reported to be an action execution and observation matching system. It also played a crucial role in the development of motor and language functions (Nishitani and Hari, 2000; Tettamanti et al., 2005). Our study illustrated that moderate-intensity exercise has a positive effect on the functions of MNS by increasing the Oxy-Hb during an OBS task. This result was consistent with Hypothesis 2 and other similar studies, which have shown the beneficial effect of moderate-intensity exercise on executive functions as indexed by the increasing Oxy-Hb (Yanagisawa et al., 2010; Byun et al., 2014). Therefore, the result of this study implied that moderate exercise might be an effective way to improve social cognition by activating the MNS. Our result was consistent with recent studies showed that moderate exercise benefited those who have social cognition deficits social behaviors such as autism spectrum disorder (ASD) (Magnusson et al., 2012; Schmitz et al., 2017), in whom an MNS deficit has been described (Theoret et al., 2005; Hadjikhani et al., 2006). fMRI studies have also suggested no mirror neuron activity in the inferior frontal gyrus (pars opercularis in children with autism during imitation of emotional expressions (Dapretto et al., 2005), as well as during observation of human motion (Martineau et al., 2010). Our study indirectly provided one of the first pieces of neural basic evidence that exercise can improve the social behaviors of children with autism by improving the activation of MNS.

In addition, the subgroup analysis also showed that moderate exercise benefited people with high and low fitness levels, but not at moderate fitness level. Thus, Hypothesis 3 was supported. Specifically, it revealed the improvement of MNS activation in high fitness levels of the PMC region and improved the MNS activation of low fitness level individuals in IFG and PMC regions under OBS task. AS we can find plenty evidence to support acute exercise improved human brain functions of high and low fit individuals, recent studies have demonstrated the positive effect of acute exercise on cognitive performance of high and low fitness group in old adults (Chang et al., 2012, 2015; Chu et al., 2015). For instance, Chu et al. (2015) recruited forty-six healthy older adults to do a reading control and Stroop tasks after 30 min aerobic exercise training, the results revealed that acute exercise improved the performance of these two types of cognitive functions in both high and low fitness level old adults. Moreover, Hogan et al. (2013) demonstrated that unfit group has lower error rates in the flanker task under the exercise condition compared with rest condition and faster RTs were observed in fit participants after exercise. Although a previous meta-analysis has reported that fitness level significantly modulated the positive effects of exercise for low fit and high fit participants after a delay following exercise (Chang et al., 2012), In contrast, Chang et al. (2014) indicated acute exercise can improve performance in the congruent condition of Stroop task in all levels of cardiovascular fitness, but individuals of high cardiovascular fitness level demonstrated longer response times under incongruent condition. More research is needed since particularly in the context that social cognition and executive function are two different brain functions. Possible explanations for this result is the different values of VO_{2max} were used in different studies to categorized different fitness levels (Chang et al., 2014), the intensity of exercise and possibly different durations of exercise protocol led to different results (Chang et al., 2012). In addition, we hypothesized that social cognition is more sensitive to the stimulation of exercise when individuals are of low cardiovascular fitness, which can be easily aroused in a short period of time. However, individuals of moderate fitness are accustomed to moderate exercise, such that they experience marginal returns on social cognition improvement. Only when individuals reach a high fitness level in a long-term training program, can social cognition enjoy the greatest benefits from exercise since our body is in an optimal condition. There were few studies that have used neuroimaging methods to investigate the effect of exercise on different aerobic fitness levels participants' cognition (Pesce, 2009). Therefore, more research is required to determine how and why moderate-intensity exercise benefits MNS in high and low fitness individuals.

Besides, PMC area as one of important MNS regions, it showed improvements of activation in both high and low fit individuals under the action understanding task (OBS). This result can be supported by previous study demonstrated the positive effect of exercise intervention on Parkinson's disease patients, they showed that exercise increased motor control in early Parkinson's disease patients (Fisher et al., 2008; Shah et al., 2016). In Petzinger et al. (2013)'s review, they summarized exercise intervention to enable the goal-based motor skill training to engage the cognitive circuit to motor learning. Exercise increased the blood flow and facilitated the neuroplasticity in elderly adults, so this has the potential to result in the improvement of both cognitive and automatic components of motor control. Thus, our study indirectly explained why exercise intervention increased the self-perceived capability through instruction and feedback (reinforcement) in Parkinson's elderly adults, which can be explained by improving the action understanding function after exercise.

We also discuss whether the exercise only improved one of the functions of MNS which is motor control. Or exercise only improved action understanding but not to reach the social cognition function. Hickok et al. (2011b) suggest that MNS was merely a motor control or action selection function, and does not include understanding action performing by oneself or others. They provided much evidence to show that information flowing down into the temporal lobes was used to connect our visual and auditory experience with memories of conceptual objects and the dorsal stream processes that same visual information to integrate with the PMC region to generate movement. As the MNS was part of this dorsal stream, the output of motor (Hickok et al., 2011a). However, previous studies also indicated perform social tasks could activate PMC regions (Buccino et al., 2001; Molnar-Szakacs et al., 2006; Perkins et al., 2015), this evidence supported MNS function involves action understanding to social recognition. Moreover, our study implied that the MNS basic function is not only a motor controller since participants remained still and simply observed the action will not requiring any extra motor control function in this process (OBS tasks), the result indicated improvements in Oxy-Hb and Deoxy-Hb in action observation task after exercise to support moderate exercise was indeed stimulating the action understanding function. Similar to the argument mentioned above, some researchers also argued that parts of MNS (dorsal part of PMC) was responded by the action understanding, but the theory of mind or social cognition function is control by MENT (dorsal part of mPFC and the IFG as another part of MNS) (Geiger et al., 2019), even this statement is true, the result from our study indicated that exercise might benefit social cognition is still valid. Since in IFG region, the activation of low-level participants was still improved.

LIMITATION AND FUTURE RESEARCH

The present study might be limited because the Oxy-Hb and Deoxy-Hb values within each fitness level between men and women were not categorized identically, this issue due to the limit number of participants in each fitness level. Therefore, these issues may limit the generalizability of our findings and future research should identify the role of sex on exercise and the MNS. However, since the factor of gender has already been counter-balanced in this study (four out of 12 were female in high fitness, six out of 13 were female in moderate, and six out of 11 were female in low fitness), we can assume that effect of gender would not bias the results.

Another question is whether we should use measures of Oxy-Hb or Deoxy-Hb to represent behavioral data. Some studies have indicated that the Oxy-Hb signal is often observed to have a higher amplitude than the Deoxy-Hb signal (Strangman et al., 2002; Yanagisawa et al., 2010), which means that Oxy-Hb is more sensitive to the task response (Cheng et al., 2015). Our study also illustrated more amplitude changes using Oxy-Hb signal compared with Deoxy-Hb. However, we were still able to observe some trace when using Deoxy-Hb in our study, which suggests that Deoxy-Hb data from fNIRS is still necessary to include in the analysis for a more comprehensive picture.

As our study only used the acute aerobic exercise protocol, and different protocols of exercise have indicated different effects on cognitive performances, expanded researches into effect of long-term exercise, and different exercise protocols of training programs are necessary to determine the effect of exercise on MNS. And more task protocols involve behavioral index associate with social cognition performance should be included into neuroimaging studies since we only used the Oxy-Hb and Deoxy-Hb as the index to indicate the effect of exercise on the MNS.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Guangzhou Sport University. 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

ZX, MH, and M-QX contributed to conception and design of the study. ZX, Z-RW, and JL organized the database. ZX and M-QX analyzed the data. ZX wrote the first draft of the manuscript. MH and M-QX contributed to manuscript revision and read and approved the submitted version.

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Correlation Between Cognition and Balance Among Middle-Aged and Older Adults Observed Through a Tai Chi Intervention Program

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Background: Age-associated decline in cognition and balance may cause severe ability loss for daily living activities among middle-aged and older adults. The relationship between cognition and balance in this aging population remains to be explored.

Objective: The present study Is exploratory in nature and aimed to examine the relationship between balance (both static and dynamic components) and global cognitive function among middle-aged and older adults through Tai Chi (TC) practice as a research avenue.

Methods: A short-term (12 weeks) intervention of TC was conducted among middle-aged and older adults in the community setting. Global cognitive function (using the Chinese version of the Montreal Cognitive Assessment score (MoCA) and balance (i.e., one leg standing test score; Timed Up and Go Test score, TUGT) of all participants were assessed before and after the intervention. Age, body mass index (BMI), sex, and physical fitness variables (Chair Stand Test, CST; the 6-Meter Walk Test, 6MWT) were also collected as confounding factors.

Results: Significant moderator effects of baseline CST on the association between the dichotomized baseline MoCA score and the baseline left leg balance score ($p = 0.0247$), the baseline right leg balance score ($p = 0.0140$) and the baseline TUGT score ($p = 0.0346$) were found. Change score of left score balance ($p = 0.0192$) and change score of TUGT ($p = 0.0162$) were found to be significantly associated with change score of cognitive function.

Conclusion: Cognitive function and balance are interrelated in middle-aged and older adults. The association between global cognitive function and balance Is moderated by strength of lower limbs. The change scores of cognitive function and balance introduced by TC training were found to be positively correlated. Future research Is warranted to further confirm the cause-effect relationship of cognitive function and balance and its influencing factors among middle-aged and older adults utilizing intervention studies with larger sample sizes.

Keywords: cognition, alternative exercise, postural control, equilibrium, Tai Chi

INTRODUCTION

A large proportion of older adults live alone or are without children of any age at home. For example, in China, half (49.7%) of those 60 years and older live with no children, and this proportion increases to 56.1% in large and medium-sized cities (China Population Press, 2015). An increasing number of older adults living alone or without children exerts financial pressure on families and society as a whole (Asian Development Bank, 2014; Whetten-Goldstein et al., 2015). Moreover, greater financial pressures are more likely when older adults lose independence in activities of daily living such as walking, feeding, dressing and grooming, toileting, bathing, transferring, cooking, transportation, and shopping, etc. (Mlinac and Feng, 2016). Fall injuries and dementia are the most frequent and costly age-induced factors that may cause complete loss of independence in activities of daily living. According to the Centers for Disease Control and Prevention, falling Is the leading cause of fatal and non-fatal injuries among older adults, and more than one fourth of adults aged 65 years or above will fall each year (CDC Newsroom, 2016). For instance, among older Americans, around 29 million falls occur each year, resulting in 3 million emergency department visits, 800,000 hospitalizations, and 28,000 deaths. The average hospital cost of a fall encounter Is over US$30,000 and the annual Medicare costs for falls for individuals residing in the US aged 65 years and above was ∼US$31 billion in the year 2015 (Laurence and Michel, 2017). According to the World Health Organization, around 50 million individuals, globally, are currently living with dementia and nearly 10 million new cases occur each year (World Health Organization [WHO], 2017). The consequences incurred by decline in cognition are as serious as those by falls among older people. Thus far, there has not been a curative treatment for dementia (Koller et al., 2016). Hence, it Is important to maintain or slow down the degrading processes of both balance and cognitive function among older adults and even at an earlier age stage (i.e., middle-aged adults) to reduce the risks of falling (Iwasaki and Yamasoba, 2015; Zou et al., 2017b, 2018a) and dementia (Morris, 2012; Petersen, 2016). A large 10-years study of middle-aged to older adults (45–70) found that cognitive decline begins in the 45–55 decade (Singh-Manoux et al., 2012). The central ability to inhibit balance destabilizing vision-related postural control processes was found among middle-aged and older adults to depend at least partially on striatal dopaminergic pathways (Cham et al., 2007). The relationship between cognitive function and balance among middle-aged and older adults calls for potentially effective interventions that might improve both cognition and balance for this population.

Physical activity or exercise (one domain of physical activity) intervention programs have been shown to delay age-related balance or cognitive decline (Chase et al., 2016; Zou et al., 2017a; Gheysen et al., 2018; Zhang et al., 2018). Tai Chi (TC) has been recognized to promote both fall-related balance ability and cognitive function in the aging population (Wayne et al., 2014; Huang et al., 2017). TC Is a mind-body exercise with special features that have shown to be effective for improving balance and cognition together. Transitions between double- and single-leg stance commonly occur throughout entire TC routines (Wayne et al., 2016) which can potentially strengthen lower-limb muscle and flexibility, improving postural control. Additionally, TC consists of relatively complex movement sequences, which may benefit practitioners with memory training opportunities. To perform such sequences smoothly and connectedly, higher-order cognition (e.g., visuospatial ability, orientation, attentional resource allocation, and executive function) Is needed. Thus, TC may help facilitate greater conscious control over the entire body. Such practice may lead to a combined promotion in cognitive function and balance over time (Liu et al., 2018, 2019; Zou et al., 2018b,c,d, 2019a; Kong et al., 2019). Therefore, TC training may be a potential research avenue for investigating the relationship of cognitive function and balance. However, previous studies that investigated the intervention effects of TC on age-related decline in cognition and balance, and that evaluated both outcomes simultaneously are limited. Recently, several large-scale epidemiological studies showed that balance and cognition are highly interdependent (Clouston et al., 2013; Smith-Ray et al., 2015; Demnitz et al., 2016). Synergistic effects on improvements in both balance control and cognitive functioning were found by exercises combining cognitive and balance training, including multimodal exercise (Marmeleira et al., 2018), unicycling training (Weber et al., 2019), and mind-body exercise like yoga (Subramaniam and Bhatt, 2017). In addition, cognitive functions were also reported to be highly associated with mobility among middle-aged and older adults (Buchman et al., 2011; Demnitz et al., 2016, 2018; Li et al., 2018). The authors of the present study conducted a randomized trial, with modified Chen-style TC as case and 24-style active TC as control, to verify the effectiveness of TC training on improving cognitive function and balance (Zou et al., 2019b). By re-exploring and pooling the data from this randomized trial, the main purpose of this study was to examine the relationship between balance (both static and dynamic components) and global cognitive function under a condition of TC training among middle-aged and older adults controlling for key covariates (e.g., age, sex, mobility level). It Is hypothesized that there would be a positive and interdependent relationship between global cognitive function and balance among middle-aged and older adults.

METHODS

Experimental Design

A 12-week intervention of TC was conducted among middle-aged and older adults. Baseline and posttest data on balance and cognitive function were collected; baseline and posttest data on confounding factors of fitness of lower limbs and aerobic exercise capacity were also collected; data on other confounding factors (i.e., age, gender, height, weight, and heart rate) were collected at baseline. Ethical approval was obtained from the research ethics committee before the commencement of this study.

Study Participants

Participants included 78 Chinese middle-aged and older adults (mean age: 58.92 ± 8.03 years) and consisted of 37 male individuals and 41 female individuals. Participants were recruited from Yongzhou city of Hunan province in China between December 2017 and March 2018. Individuals who had no physical limitations in participating in TC practice and had not received any exercise training programs or practiced TC regularly over the past 3 months were included. Those individuals who reported serious diseases (e.g., cardiovascular disease, clinical depression) or a history of alcohol abuse, and who were not able to understand and follow the instructions in the pilot training session were excluded. All participants voluntarily participated in this study and provided written informed consent.

Tai Chi Intervention Program

The intervention was a 12-week TC program consisting of two phases. All participants attended training for 1 h per session (including 10 min of warm-up, 40 min of TC practice, and 10 min of cool-down), 3 sessions per week for the first 6 weeks in a public park in the community of the city. The purpose of the first 6-week of the intervention was to guarantee that all participants understood the instructions and mastered the essentials of TC movements. The duration and frequency of practice were progressively increased during the last 6 weeks. During the latter half of the intervention, participants trained for one, and a half hours (including 10 min of warm-up, 70 min TC practice, and 10 min cool-down) in each session, five sessions per week for 6 weeks. In total, all participants practiced TC for 2,820 min over 12 weeks in a group format (∼40 participants per class). The postures involved in TC practice were from two different TC styles (modified Chen-style and 24-style) with different difficulty levels. The intervention was led by one experienced TC instructor with more than 15 years of TC experience. The comparisons of the intervention effects between these two TC styles have been reported elsewhere (Zou et al., 2019b). The present study focuses on investigating correlations between improvements of cognition and balance through the TC intervention program and therefore the two TC groups were pooled together.

Outcome Measures

Global Cognitive Function

Global cognitive function was assessed using the Bejing version Montreal Cognitive Assessment (MoCA)[1] that has been used in Chinese in previous research (Lu et al., 2011). The MoCA Is a validated brief paper-and-pencil screening test for cognitive function and detecting cognitive impairments. It consists of 12 elements to assess a variety of cognitive domains, including visuospatial ability, attention, executive function, language, orientation, memory, and abstraction. The total score of MoCA ranges from 0 to 30, with high scores representing high global cognitive ability and a score of <26 considered as experiencing symptoms of cognitive impairments.

Balance

The one leg standing test was used to evaluate static balance in unilateral stance. With their eyes closed, the participants were instructed to stand on the leg they selected, lift the knee of the other leg to ∼90°, keep their arms by their sides, and maintain balance without any assistive device. Both legs were tested successively with three attempts for each leg. To prevent falls or injuries, the tester stood close to the participants throughout the trials. The test was over when either the stance foot shifted or when the lifted foot was placed on the ground. The stance duration (in seconds) for each leg in each attempt was recorded using a stopwatch and the best (longest) score was chosen and included for data analyses (Michikawa et al., 2009).

The Timed Up and Go Test (TUGT), which Is widely used in elderly populations, was used to measure dynamic balance. The TUGT measures the time taken by an individual to rise from a standard chair (with the height of ∼45 cm), walk three meters, turn around, walk back to the chair, and sit down without any assistive device throughout. The participants were asked to be seated on the chair with their arms resting on the chair's arms, and then stand up on the word "go" command. The recording time started on the "go" command and stopped as the participant sat down (Chan et al., 2017). Each participant had three attempts with the best (fastest) attempt used in the analysis.

Confounding Variables

Each participant provided demographic information in a survey, including age and sex. Participants' heart rate (HR), body height and weight (Healthometer 402 KL Beam Scale weight/Height Rod, PELSTAR, McCook, IL, United States) were assessed at baseline. Body mass index (BMI; kg/m^2) was calculated. The performance of balance has been widely reported as closely related to individuals' physical mobility and fitness level (Nakano et al., 2014). Chair Stand Test (CST) and the 6-Meter Walk Test (6MWT) were used to assess the strength of lower limbs

[1] www.mocatest.org

and aerobic endurance, respectively, at baseline and immediately after the intervention (12 weeks), and therefore considered as confounding factors in this study regarding the relation between cognition and balance. These two tests have been used in the elderly population, with further details discussed elsewhere (Zhou et al., 2019).

Statistical Analysis

All statistical analyses were carried out using R (version 3.6.1) (R Core Team, 2019). First, associations between the baseline score of the cognitive parameter MoCA and the baseline score of each of the three balance parameters, namely, left leg balance, right leg balance, and TUGT were assessed using regression analysis to control for potential confounders, with interaction effects between balance parameters and confounding variables considered. As the baseline MoCA scores in the present data were not normally distributed (Shapiro–Wilk Normality Test statistic $W = 0.94$, $p = 0.0007$), they were dichotomized at a recommended clinical cutoff of 26 (coded as 1 or normal: MoCA score ≥26; coded as 0 or cognitive impairment: MoCA score < 26) (Hu et al., 2013). The varImp (abbreviation for "variance importance") function of the caret package (version 6.0–84) in R was used to report the relative raw importance of all the available factors in the data that are potentially correlated to the dichotomized baseline MoCA, based on main-effect-only logistic regression model (Gevrey et al., 2003). Then three logistic regression analyses were used, with the dependent variable being the dichotomized baseline MoCA score, and independent variables being each of the three baseline balance parameters (i.e., Left Leg Balance score, Right Leg Balance score, or TUGT score) respectively, plus all of the six confounding variables (i.e., Gender, Age, HR, BMI, CST, and 6MWT), as well as their interaction terms with the corresponding baseline balance parameter. Second, four paired-sample t-tests were carried out to assess the change score volume of MoCA, left leg balance, right leg balance, and TUGT across time. Third, associations between the change score of MoCA and the change score of each of the three balance parameters were assessed by three linear regression models, controlling for change score of CST, change score of 6MWT, Gender, Age, HR, and BMI.

RESULTS

Seventeen out of the total 78 participants in this study were classified as having cognitive impairment (i.e., with MoCA score <26). The characteristics of all participants and descriptive information of confounding variables are presented in **Table 1**. Mean and standard deviation (M ± SD) of the raw data on all outcome measures at baseline and post-intervention, as well as the corresponding paired t-test results for these pre and post intervention data are presented in **Table 2**. All parameters were improved after the TC intervention. No participant had MoCA score less than 26 after the TC intervention. As noted earlier, these paired *t*-test results of significant improvements of cognitive function and balance introduced by TC intervention listed in **Table 2** have already been confirmed with a different statistical method (i.e., the generalized estimation equations) for randomized trials on these data in a previously published paper (Zou et al., 2019b). Therefore, these significant results are not new but consistent findings with different type of test statistic.

TABLE 1 | Confounder information of study participants at baseline and posttest (*N* = 78).

Variable	Distribution	
Gender	**Baseline**	**Posttest**
Male (*n*)	37	
Female (*n*)	41	
Age (years)	58.92 ± 8.03	
Heart Rate (HR)	74.51 ± 7.13	
Body mass index (BMI) (kg/m^2)	24.61 ± 2.42	
Chair stand test (CST)	9.36 ± 2.14	8.39 ± 1.61
6-meter walk test (6MWT)	5.12 ± 0.99	4.93 ± 0.83

Sample frequencies are displayed for each level of categorical variable; sample mean and standard deviation are displayed for each continuous variable as the form of "M ± SD".

TABLE 2 | Cognitive function and balance data at baseline and posttest, and their paired *t*-test results.

Variable	Baseline	Posttest	Paired *t*-test statistic	*p*
Global cognitive function (MoCA)	26.41 ± 1.40	29.86 ± 0.45	22.81	< 2.2e–16 ***
Static balance (left leg balance)	3.72 ± 2.54	5.63 ± 3.14	11.81	< 2.2e–16 ***
Static balance (right leg balance)	3.61 ± 2.82	5.46 ± 2.92	9.86	2.62e–15***
Dynamic balance (TUGT)	10.10 ± 2.47	8.95 ± 1.81	–9.01	1.16e–13***

*Sample mean and standard deviation are displayed for the data as the form of "M ± SD"; Significance code: '***'p < 0.001.*

Raw Relationships Between Cognitive Function *and* Balance Parameters *at* Baseline

Estimated logistic regression coefficients corresponding to the associations between the dichotomized baseline MoCA score and the baseline balance parameter scores controlling for other covariates with interaction terms are presented in **Table 3**. Similar significant tendencies were found for the correlations between the cognitive function and each of the three balance scores. A significant and positive (0.235) interaction effect between left leg balance and CST was found (95% CI 0.030–0.441, $p = 0.0247$) combined with the positively (3.287) estimated coefficient of the main effect of left leg balance score, this finding implies that high physical fitness Is associated with high positive correlation between the global cognitive function and the left leg balance. A significant and positive (11.922) coefficient estimate of the

TABLE 3 | Results of association analysis between the baseline MoCA and baseline balance scores.

Dependent variable	Dichotomized MoCA					
Independent variable	**Left leg balance**		**Right leg balance**		**TUGT**	
	Coef.	***p***	**Coef.**	***p***	**Coef.**	***p***
Balance	3.287	0.3639	11.922	0.0261*	−4.806	0.1914
Balance*HR	0.001	0.9756	−0.062	0.1821	0.031	0.3857
Balance*Gender	0.528	0.2097	−0.250	0.5874	−0.635	0.1613
Balance*Age	0.002	0.9468	−0.078	0.1166	0.057	0.1769
Balance*BMI	−0.189	0.0686	−0.187	0.1484	0.017	0.8864
Balance*CST	0.235	0.0247*	0.242	0.0140*	−0.274	0.0346*
Balance*6MWT	−0.252	0.1944	−0.130	0.6209	0.355	0.1213

MoCA; The Chinese version of the Montreal Cognitive Assessment; BMI, body mass index; CST, Chair Stand Test; TUGT, Timed Up and Go Test; Significance code: ''p < 0.05.*

TABLE 4 | Results of the association between the change scores of MoCA and those of the balance parameters.

Dependent Variable	MoCAΔ					
Independent Variable	**Left leg balanceΔ**		**Right leg balanceΔ**		**TUGTΔ**	
	Coef.	***p***	**Coef.**	***p***	**Coef.**	***p***
BalanceΔ	0.251	0.0192*	−0.025	0.7985	0.349	0.0162*
6MWTΔ	0.106	0.5693	0.069	0.7229	−0.050	0.7937
CSTΔ	−0.120	0.3866	−0.105	0.4812	−0.208	0.1507

Δ: change score; Significance code: ''p < 0.05.*

main effect of right leg balance score was found (95% CI 1.418–22.425, p = 0.00261), implying a significantly positive correlation between the global cognitive function and the right leg balance; a significant and positive (0.242) interaction effect between right leg balance and CST was also found (95% CI 0.049–0.435, p = 0.0140), implying that high physical fitness Is associated with high positive correlation between the global cognitive function and the left leg balance. A significant and negative (−0.274) interaction effect between TUGT and CST was found (95% CI −0.528 to −0.020, p = 0.0346) combined with the negatively (−4.806) estimated coefficient of the main effect of CST score, this finding implies that high physical fitness Is associated with high positive correlation between the global cognitive function and the dynamic balance (note that low TUGT score stands for high balance ability). These results indicate that the association between the baseline global cognitive function and the baseline static and dynamic balance abilities both increase with increased strength of lower limbs among middle-aged and older adults.

Relationship Between Improvements *in* Cognitive Function *and* Balance After TC Intervention

The associations between the change score of MoCA and the change score of each of the balance parameters are presented in **Table 4**. These associations are represented by regression coefficients and their p-values. As comparisons, we also provide association results between the change score of MoCA and the change scores of physical fitness parameters (CSTΔ and 6MWTΔ). The association between the change score of MoCA and the change score of left leg balance Is significantly positive with the corresponding regression coefficient estimated as 0.251 (95% CI 0.046–0.457, p = 0.0192). The association between the change score of MoCA and the change score of TUGT Is significantly positive with the corresponding regression coefficient estimated as 0.349 (95% CI 0.071–0.626, p = 0.0162). The change score of right leg balance, as well as the change scores of physical fitness parameters (CSTΔ and 6MWTΔ) do not present significant associations with change score of MoCA. These results indicate that the improvement of cognitive function introduced by TC training among middle-aged and older adults Is associated with change of left leg static balance and dynamic balance, but not with change of right leg static balance and physical fitness.

DISCUSSION

The primary purpose of this study was to investigate the dynamic relationship between cognitive function and balance among middle-aged and older adults through TC practice while considering influencing factors such as physical fitness (i.e., strength of lower limbs and aerobic endurance). Major findings of this study include: (1) cognitive function was related to static and dynamic balance, and such correlation increases with increased strength of lower limbs; (2) Improvements in cognitive function Is also potentially associated with improvements in left leg (usually non-dominant leg) static balance and dynamic balance, but not associated with improvements in right leg (usually dominant leg) balance and physical fitness introduced by TC training.

Cognitive function and balance remarkably decline with advancing age, which often restricts participation in activities of daily living and may contribute to secondary health risks (e.g., falls) in the elderly. In line with previous studies (Pichierri et al., 2011; Alonso et al., 2016), we found that cognitive function and balance are interrelated among middle-aged and older adults. This relationship can be explained by the competition of limited central attentional resources in maintaining posture and performing cognitive tasks during activities of daily living. Moreover, when compared to young individuals, middle-aged, and older adults usually experience more cognitive distractions and spend more attentional resources in generating complex movements due to the natural ageing process (Pichierri et al., 2011). Additionally, the results in this study demonstrated the importance of muscle strength as a moderator for the relationship between improvement of cognition and that of balance among middle-aged and older adults, which Is consistent with previous literature that muscle strength serves as an important role in performing activities requiring balance and cognitive functioning (Alonso et al., 2016), and that low levels of muscle training or physical activity are a risk factor for cognitive functioning or balance in middle-aged and older adults (Holviala et al., 2006; de Souto Barreto et al., 2016).

There Is a growing interest in merging physical and cognitive stimulation (mind-body exercise), such as TC and Yoga, in health promotion in aging individuals (Ni et al., 2014; Gothe et al., 2016; Marmeleira et al., 2018). Furthermore, a recent systematic review suggested that interventions incorporating both physical and cognitive components not only benefit cognitive function, but also physical functions, including balance (Booth et al., 2016). In the present study the association of cognitive function with balance through a TC intervention program Is comparable to a cross-sectional study (Leandri et al., 2015) that evaluated cognitive function using MoCA and static balance with participants eyes closed (similar to the present study). The study found a significant association between static and dynamic balance and cognitive function in middle-aged and older adults. These findings suggest that this relationship may due to the link between the vestibular system and the hippocampus in memory performance. Future research, using neuroimaging techniques, should investigate this in future.

The major strengths of this study include the assessment of both cognitive function and balance with the consideration of other key confounding factors and the advanced statistical analyses. Although this study was exploratory in nature, these findings will add to the current literature by improving our understanding of the relationship between cognitive function and balance and the mechanism behind the beneficial effects of TC on cognition. Such research will be valuable to professionals and practitioners who have concerns with the prevention and treatment of age-related deterioration in cognitive and physical functioning in the elderly.

Despite the above advantages, findings from this study must be interpreted in light of its limitations. First, MoCA evaluates global cognitive function as a diagnostic measurement, which may lack some degree of sensitivity to TC training. In addition, the dichotomization of the MoCA variable in the study may also limit its sensitivity to TC training, or perhaps over-emphasizes its effect. Future studies should focus on the specific components of cognitive function, such as executive function and memory. Second, all participants were Chinese, which limits the generalizability of our findings to other non-Chinese populations.

CONCLUSION

Cognitive function and balance are interrelated in middle-aged and older adults when using TC practice as a new research avenue for this investigation. The global cognitive function Is associated with balance, and such association Is moderated by strength of lower limbs. Trainings or exercise forms designed for improving balance may be also likely facilitate cognitive function among middle-aged and older adults. Future research Is warranted to further confirm the cause-effect relationship of cognitive function and balance among middle-aged and older adults and its influencing factors in intervention studies with larger sample size.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hunan University of Science and Technology College of Sport Science Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JY, TX, and ZZ: conceptualization. TX, JY, and LY: methodology. TX: formal analysis. TX, LY, LS, JY, PL, NV, ZZ, and JY: writing – original draft preparation and writing – review and editing.

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Cardiorespiratory Fitness, Age, and Multiple Aspects of Executive Function Among Preadolescent Children

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Cardiorespiratory fitness (CRF) and age have been positively associated with children's executive function; however, few studies have simultaneously assessed the associations between both variables and different aspects of executive function among preadolescent children. Therefore, the purpose of the current study was to evaluate the simultaneous influence of CRF and age on three aspects of executive function. Preadolescent children's (n = 338) CRF levels were estimated based on the Progressive Aerobic Cardiovascular Endurance Run (PACER) test and then grouped into two age groups (Young Group: 9–10 years old and Old Group: 11–12 years old). Hierarchical multiple regression analyses were conducted for the 2-back task, the Flanker task, and the Local-Global task to assess the influence of CRF and age on working memory, inhibitory control, and shifting, respectively. Preadolescent children with greater CRF levels were associated with higher response accuracy during the 2-back task and shorter response time across congruent and incongruent conditions of the Flanker task, whereas older children showed generally superior cognitive performance. Notably, only the Old Group's CRF was positively correlated with the accuracy in the switching condition of the Local-Global task. These findings suggest that CRF or age was generally associated with better performances in working memory and inhibitory control aspects of executive function. Furthermore, the positive influence of CRF on shifting may be modulated by developed cortical maturation.

Keywords: executive function, working memory, inhibitory control, shifting, maturation, Progressive Aerobic Cardiovascular Endurance Run, cardiorespiratory fitness

INTRODUCTION

Cardiorespiratory fitness (CRF), the direct indicator of individuals' cardiovascular and respiratory systems' overall capacity to perform physical activities, plays a critical role regarding physiological and psychological health. A higher CRF level has been linked to a lower metabolic syndrome risk and a cardiovascular disease risk (Twisk et al., 2000; Padilla-Moledo et al., 2012), increased volumes of certain cortical regions [e.g., the gray matter volume of the hippocampus and the basal ganglia (Chaddock et al., 2010a,b)], and lower risks of depression and anxiety (Biddle and Asare, 2011). The beneficial effects associated with higher CRF levels have been extended to academic performance in preadolescent school-aged children (Donnelly et al., 2016; Ruiz-Ariza et al., 2017; Chu et al., 2019). These improvements are possibly caused by CRF-related enhanced executive function, which is one of the foundations of academic performance (Hillman et al., 2009, 2014; Pontifex et al., 2011; Voss et al., 2011; Scudder et al., 2016; DiPietro et al., 2019).

Executive function is a top-down and meta-cognitive function required for conducting complex and goal-oriented operations. It consists of three distinct aspects: working memory, inhibitory control, and shifting (Miyake et al., 2000). Working memory, also known as updating, has been defined as the capacity of temporarily retaining relevant information and enables individuals to manipulate or further process this information (Miyake et al., 2000; Baddeley, 2012). Inhibitory control, also known as inhibition, refers to an individual's ability to deliberately control, inhibit, or override a prepotent response or the ability to ignore irrelevant information or interferences in the environment and focus on relevant information. Shifting, also known as cognitive flexibility, represents the switching of attention or response strategies between mental sets according to the task demands (Miyake et al., 2000). These three aspects of executive function are highly important to preadolescent children's learning and academic achievement (Kao et al., 2017a; Lippi et al., 2020).

A few studies have explored the associations between CRF and these three aspects of executive function separately (Tomporowski et al., 2015). Specifically, children with higher CRF assessed by the field-based CRF assessment [e.g., Progressive Aerobic Cardiovascular Endurance Run (PACER)] were associated with a superior performance on working memory capacity (Scudder et al., 2014, 2016). Cross-sectional research using the laboratory-based CRF assessment also revealed similar positive links between maximal oxygen consumption (VO_{2max}) and working memory capacity (Kamijo et al., 2011; Drollette et al., 2016; Kao et al., 2017b). Similarly, cross-sectional studies utilizing either field-based (e.g., PACER) or laboratory-based (e.g., VO_{2max}) CRF assessments to explore the associations between CRF and inhibitory control have revealed positive associations between CRF levels and task performance [e.g., shorter response times (Scudder et al., 2014; Drollette et al., 2016; Song et al., 2017) or higher response accuracy (Hillman et al., 2009; Pontifex et al., 2011; Scudder et al., 2014)], especially during the task condition requiring a more substantial amount of inhibitory control. Finally, similar findings of the beneficial effects of CRF on the shifting aspects of executive function have also been documented (Ishihara et al., 2018; Westfall et al., 2018).

Although relatively consistent evidence suggests a positive association between CRF and executive function, several potential limitations should be noted. First, prior studies examining the relationships between CRF and executive functions of children mainly used combined data across different age groups (e.g., aged 10–18 years) (Hillman et al., 2006; Themanson et al., 2006; Scudder et al., 2014; Kao et al., 2017b). Importantly, the cortical maturation trajectory of different parts of the brain are not uniform and, consequently, the development trajectory of various aspects of executive function might differ from each other during early childhood (Best and Miller, 2010; Diamond, 2013). It is plausible that the capability of completing the cognitive tasks increases while the structural and functional development continuously progresses throughout adolescence into early adulthood in which the associations between CRF and executive function might be altered in different age groups of preadolescent children. Due to the complex laboratory-based CRF assessment and neuro-electrical equipment, the sample sizes in prior research were relatively small and less representative (Scudder et al., 2014). Finally, relatively few studies have simultaneously compared the various aspects of executive function among preadolescent school-aged children.

Accordingly, the current research aims to examine how CRF and age influence the three aspects of executive function – working memory, inhibitory control, and shifting – in a large sample of preadolescent school-aged children. It was hypothesized that the children with higher levels of CRF or at older ages might be associated with superior executive function as reflected in better cognitive task performance, and then the interactions between CRF and age would be observed.

MATERIALS AND METHODS

Participants

For this study, 377 school-aged preadolescent children were initially recruited. Eligible participants were screened by having to meet the following inclusion criteria: (1) age between 9 and 12 years old; (2) no history of psychiatric or neurological disease; (3) the anxiety scores assessed by the Chinese version of Self-Rating Anxiety Scale (Zung, 1971) were less than 50; (4) the depression scores assessed by the Chinese version of Children's Depression Inventory (Yu and Li, 2000) were less than 19; (5) the scores of the modified Chinese version of Raven's Standard Progressive Matrices were above the moderate levels; and (6) no history of cardiovascular disease.

Only those who completed the CRF and executive function assessments were included in the final analytical study. Three hundred thirty-eight children were finally recruited and grouped into the Young Group (9–10 years) and the Old Group (11–12 years) (**Table 1**).

The study was approved by the Institutional Review Board of East China Normal University, China. The written informed consent was obtained from children and their legal guardians before the children participated in the experiment.

CRF Assessment

In the current study, the PACER test, a multistage 20-m shuttle run test, was utilized to assess children's CRF performance. The PACER test is considered valid for accurately measuring CRF for wide age ranges of participants, and it has been utilized in several prior studies that examined the association between CRF and cognitive and academic performance (Scudder et al., 2014, 2016). The test-retest reliability (r = 0.72–0.89) and validity (r = 0.51–0.84) of the PACER have been well documented previously (Leger et al., 1988; Mahoney, 1992; Yu and Fang, 2002).

TABLE 1 | Preadolescents' demographic and cognitive-related characteristics of the Young and the Old Groups (mean ± SD).

Variables	Young Group	Old Group
No. of participants (% male)	150 (62.7%)	188 (64.9%)
Mean age (years)	9.49 ± 0.50	11.37 ± 0.48
Height (m)	1.37 ± 0.07	1.48 ± 0.08*
Weight (kg)	30.07 ± 5.70	36.88 ± 7.99*
BMI ($kg.m^{-2}$)	16.02 ± 2.10	16.73 ± 2.47*
Estimated VO_{2max} ($ml.kg^{-1}.min^{-1}$)	49.77 ± 3.48	46.71 ± 3.76*
Anxiety score	37 ± 6.36	42 ± 6.31
Depression score	12.35 ± 4.48	11.64 ± 4.58
Raven's Standard Progressive Matrices score	53.7 ± 9.7	55.53 ± 3.63
2-back task		
RT (ms)	1190.08 ± 242.9	1081.41 ± 230.09*
Accuracy	0.70 ± 0.17	0.79 ± 0.17*
Flanker task		
Congruent RT (ms)	486.43 ± 108.71	463.37 ± 106.29
Congruent accuracy	0.69 ± 0.19	0.70 ± 0.19
Incongruent RT (ms)	503.47 ± 118.1	470. 67 ± 115.64*
Incongruent accuracy	0.65 ± 0.19	0.67 ± 0.19
Local-Global task		
Non-switching RT (ms)	901.65 ± 293.26	836.14 ± 242.53*
Non-switching accuracy	0.90 ± 0.15	0.91 ± 0.14
Switching RT (ms)	1100.84 ± 332.42	1050.04 ± 275.63
Switching accuracy	0.86 ± 0.14	0.86 ± 0.14

VO_{2max}, maximal oxygen consumption; RT, response time.$p \leq 0.05$.*

The PACER test was administrated during participants' second visits by the trained physical education teachers following the standardized protocol (Welk and Meredith, 2008). Briefly, participants were instructed to perform a 5-min standardized warm-up, following run back and forth from one maker to another marker spaced 20-m apart while keeping pace with the prerecorded cadence. The frequency of beat increases 0.5 km/h every minute, with an initial speed of 8.5 km/h. Participants were encouraged to keep up with the beat for as long as possible. The test was terminated if the given participant failed to traverse the 20-m distance between the markers within the designated time twice or was no longer able to maintain the pace and voluntarily stopped. The higher the number of laps a participant completed, the higher the CRF level they had.

Based on the number of the laps a child completed, the index of CRF (i.e., the estimated VO_{2max}) was calculated using the following equation (Leger et al., 1988):

VO_{2max} ($ml.kg^{-1}.min^{-1}$) = 31.025 + 3.238 × speed (speed corresponding to the final stage in $km.h^{-1}$) − 3.248 × age (years) + 0.1536 × age × speed

2-Back Task

The working memory aspect of executive function was assessed by the 2-back task that was programmed and ran using the E-prime software (v. 2.0, Psychology Software Tools, Inc.). The 2-back task is a modified *N*-back task, which has been a widely utilized paradigm to assess the capacity of working memory (Scudder et al., 2016; Ishihara et al., 2017). The 2-back task consisted of a sequence of white numeric digits (1–9), each measuring 1.5 cm × 1.5 cm. The stimulus was presented focally against a black background with a duration of 2,000 ms and a fixed intertrial interval of 3,000 ms. The task was composed of two blocks of 25 trials each, with 60 s of rest between the blocks. The total duration of the tasks summed to about 7 min. The participants were instructed to press the #1 key on the numeric keypad if the current stimulus (trial n) was matched to the stimulus two trials earlier (trial $n-2$); otherwise, they were instructed to press the #2 key. Trials of 50% probability as represented required the participants to press the #1 key as the correct response. The primary behavioral indices were the response times of the correct responses and response accuracy.

Flanker Task

The inhibitory aspect of executive function was assessed by the modified Flanker task (Eriksen and Eriksen, 1974; Pindus et al., 2019) that was programmed and ran using the E-prime software. Each trial of the Flanker task consisted of a row of five parallel white arrows presented in the center of a 14″ LCD screen against a black background. The target arrow was posited in the middle, and two distractive arrows were on each side of the target arrow (flankers). Each trial appeared for 200 ms and then followed by a randomly selected various intertrial interval of 1,250–1,500 ms.

The Flanker task consisted of two types of trials: (1) the congruent trials (50%), in which the directions of all the arrows were the same (e.g., < < < < < or > > > > >) and (2) the incongruent trials (50%), in which the target arrow was pointed in the opposite direction from the flankers (e.g., < < > < < or > > < > >). The trials were separated into two blocks of 75 trials each, with 60 s of rest between the blocks. The overall number of congruent and incongruent trials were equal across the two blocks (50% of trials were congruent). The participants were instructed to press either the #1 or #2 key on the numeric keypad corresponding to the direction of the target arrow (left or right, respectively), as fast and accurately as possible.

If the participants responded within 200 ms, the stimuli disappeared, and the screen remained black for the rest of the 200 ms period. The response times of correct responses and response accuracy for congruent and incongruent conditions were recorded and assessed as the primary behavioral indices.

Local-Global Task

The shifting aspect of executive function was assessed by the modified Local-Global task (Ishihara et al., 2018) that was programmed and ran using the E-prime software. The Navon-like global/local figures (Navon, 1977) were utilized during the task as the stimuli was made of two target numeric digits (i.e., the numeric digit 1, and 2) and two neutral distractors (i.e., the numeric digit 3 and 4). The large global numeric digits (global level) consist of copies of small local numeric digits (local level), and all of the numeric digits were presented equally at the global and local levels. For instance, 25% of the global numeric digits were the target numeric digit 1, which might be composed of one of the local distractor numeric digits. Similarly, 25% of the local numeric digits were the target numeric digit 1, which could be organized to form the global distractor numeric digits.

The switching condition (i.e., the target numeric digits were switched from local to global levels or vice versa) consisted of 46.8% of the trials. On the other hand, the repetitive non-switching condition (i.e., the current target numeric digit and the previous target were at the same level; e.g., a target "global" numeric digit 2 followed by a target "global" numeric digit 1) accounted for 53.2% of the trials. Two blocks of 36 trials each were presented, with 60 s of rest between the blocks. The stimuli presented focally on a 14″ LCD screen would disappear soon after the participants made their responses, and the next stimulus appeared immediately. Participants were instructed to press the #1 key or the #2 key on the numeric keypad when they identified the presence of target stimuli (the numeric digit 1 or the numeric digit 2, respectively) at either the global level or the local level. The stimuli remained on the screen until a response was made. The response time for a correct response and the accuracy of the switching and repetitive non-swathing conditions were the main behavioral indices.

Procedures

Each eligible child participated for 3 separate days to complete the study. On their first visit, the children and their legal guardians completed the written informational concerns in a quiet indoor space. Additionally, their basic demographic data (e.g., gender, age, height, and weight) were collected or assessed. On their second visit, their CRF was assessed by the PACER test. On their third visit, three computer-based cognitive tasks were completed in a fixed order that lasted for an hour, with short breaks between cognitive tasks. The order of tests was as follows: the 2-back task, the Flanker task, and the Local-Global task. Before starting the formal cognitive tasks, the participants received detailed instructions regarding each cognitive task and have achieved at least 80% accuracy of the practice trials. Given the large number of children recruited for the current study, the primary researchers conducted the experiment during both morning and afternoon hours.

Statistical Analysis of Data

Descriptive statistics were calculated to summarize the baseline characteristics of the participants. A series of independent *t*-test were further conducted by assessing the differences between the demographic and cognitive-related data by age group.

Separate 2-step linear hierarchical regression analyses were performed for two indices from the 2-back task (correct target response time/accuracy), and four indices from the Flanker task (correct congruent response time/accuracy and correct incongruent response time/accuracy), and four indices from the Local-Global task (correct switching response time/accuracy and correct non-switching response time/accuracy).

To examine the contributions of CRF, age, and their interactions on the three aspects of executive function, the variables were entered into the regression model in the following order: (1) CRF estimated from PACER laps, age group (coded as 0 for the Young Group and 1 for the Old Group), and body mass index (BMI) (Step 1) and (Step 2) the interactions between CRF and the age group (Step 2). If a significant interaction between CRF and an age group was detected, a simple slope analysis (Aiken et al., 1991) was performed to examine the main effects of CRF on the Young Group and the Old Group. The multiple regression coefficients squared R^2 for the overall model (R^2), the stepwise changes in R^2 (ΔR^2), and the standardized regression weight (β) for each predictor variable were reported. A significance level of $p < 0.05$ was set.

All statistical analyses were conducted using the SPSS® 21 statistical package (IBM Corporation, Armonk, NY, USA).

RESULTS

Participants Characteristics

Independent *t*-test of the demographic data revealed that the participants in the Old Group were taller, heavier, and had larger BMI values than the participants in the Young Group (ps < 0.05). The Old Group also had lower estimated VO_{2max} values than the Young Group ($p < 0.05$). None of the other demographic variables were significantly different between the two groups (all ps > 0.05) (**Table 1**).

Independent *t*-test of the cognitive-related measures revealed that the Old Group had shorter response times and higher accuracy in the 2-back task, shorter response times in the incongruent Flanker task condition, and shorter response times in the non-switching Local-Global task condition than the Young Group (ps < 0.05). None of the other cognitive-related measures were significantly different between the two groups (all ps > 0.05).

CRF, Age, and 2-Back Task

Regarding the response time, the regression analysis revealed a significant overall model effect of Step 1 ($\Delta R^2 = 0.06$, $p < 0.01$), with a significant negative effect for age ($\beta = -0.25$, $p < 0.01$) (**Table 2**). The overall model effect of Step 2 was not significant ($p = 0.79$); however, a significant negative effect for age ($\beta = -0.26$, $p < 0.01$) was observed.

Regarding the response accuracy, the overall model effect of Step 1 was significant ($\Delta R^2 = 0.07$, $p < 0.01$), with a significant positive effect for CRF ($\beta = 0.13$, $p = 0.04$) and for age ($\beta = 0.29$, $p < 0.01$). The overall model effect of Step 2 was not significant ($p = 0.12$); however, a significant positive effect for age ($\beta = 0.28$, $p < 0.01$) was observed.

CRF, Age, and Flanker Task

Regarding the response time of the congruent condition, the overall model effect of Step 1 was significant ($\Delta R^2 = 0.03$, $p < 0.01$), with significant negative effects for CRF ($\beta = -0.16$, $p < 0.01$) and for age ($\beta = -0.16$, $p < 0.01$) (**Table 2**). The overall model effect of Step 2 was not significant ($p = 0.23$); however, a significant positive effect for age ($\beta = -0.15$, $p = 0.01$) was observed. Regarding the response accuracy of the congruent condition, neither the overall model effects of Step 1 and Step 2 nor other variables (CRF, age group, and BMI) were significant (all ps > 0.05).

Regarding the response time of the incongruent condition, the overall model effect of Step 1 was significant ($\Delta R^2 = 0.04$, $p < 0.01$), with significant negative effects for CRF ($\beta = -0.13$, $p = 0.03$) and age ($\beta = -0.17$, $p < 0.01$). The overall model effect of Step 2 was not significant ($p = 0.22$); however, a significant negative effect for age ($\beta = -0.16$, $p = 0.01$) was observed. Regarding the response accuracy of the incongruent condition, neither the overall model effects of Step 1 and Step 2 nor other variables (CRF, age group, and BMI) were significant (all ps > 0.05).

TABLE 2 | Regression analysis for the associations between cardiorespiratory fitness, age, the 2-back task, and the Flanker task.

Model and variable	2-back task		Flanker task			
			Congruent		Incongruent	
	ΔR^2	β	ΔR^2	β	ΔR^2	β
Response time						
Step 1	0.06**		0.03**		0.04**	
CRF		−0.06		−0.16**		−0.13*
Age		−0.25**		−0.16**		−0.17**
BMI		0.03		−0.08		−0.10
Step 2	<0.001		0.004		0.004	
CRF		−0.08		−0.08		−0.04
Age		−0.26**		−0.15**		−0.16**
BMI		0.04		−0.09		−0.11
CRF × Age		0.02		−0.10		−0.11
Accuracy						
Step 1	0.07**		0.002		0.003	
CRF		0.13*		0.02		0.01
Age		0.29**		0.03		0.06
BMI		0.03		0.03		0.01
Step 2	0.01		0.002		0.001	
CRF		0.02		0.08		0.05
Age		0.28**		0.04		0.06
BMI		0.03		0.03		0.01
CRF × Age		0.13		−0.07		−0.05

*BMI, body mass index; CRF, cardiorespiratory fitness.*p ≤ 0.05; **p ≤ 0.01.*

TABLE 3 | Regression analysis for the associations between cardiorespiratory fitness, age and Local-Global task.

Model and variable	Non-switching		Switching	
	ΔR^2	β	ΔR^2	β
Response time				
Step 1	0.02		0.01	
CRF		−0.07		0.01
Age		−0.15**		−0.09
BMI		0.02		0.04
Step 2	0.001		0.003	
CRF		−0.12		0.07
Age		−0.16**		−0.08
BMI		0.02		0.04
CRF × Age		0.06		−0.09
Accuracy				
Step 1	0.002		0.01	
CRF		0.01		0.08
Age		0.01		0.02
BMI		0.05		0.04
Step 2	0.003		0.01*	
CRF		−0.06		−0.07
Age		−0.001		0.01
BMI		0.05		0.05
CRF × Age		0.09		0.19*

*BMI, body mass index; CRF, cardiorespiratory fitness.*p ≤ 0.05; **p ≤ 0.01.*

CRF, Age, and Local-Global Task

Regarding the response time of the non-switching condition, the overall model effect of Step 1 was not significant ($\Delta R^2 = 0.02$, $p = 0.07$); however, a significant negative effect for age ($\beta = -0.15$, $p < 0.01$) was observed (**Table 3**). The overall model effect of Step 2 was not significant ($p = 0.51$); however, a significant negative effect for age ($\beta = -0.16$, $p < 0.01$) was observed. Regarding the response accuracy of the non-switching condition, neither the overall model effects of Step 1 and Step 2 nor the effects of the variables (CRF, age group, and BMI) were significant (all ps > 0.05).

Regarding the response time of the switching condition, neither the overall model effects of Step 1 and Step 2 nor the effects of the variables (CRF, age group, and BMI) were significant (all ps > 0.05). Regarding the response accuracy of the switching, neither the overall model effects of Step 1 nor the effects of the variables (CRF, age group, and BMI) were significant (all ps > 0.05). However, the overall model effect of Step 2 was significant ($\Delta R^2 = 0.01$, $p = 0.03$), with a significant positive effect for the interaction of CRF and age ($\beta = 0.19$, $p = 0.03$). Further decomposition of the interaction by the single slope analysis for each age group was carried out to test the significance of predicting the accuracy of CRF. The results revealed that CRF levels significantly associated with the higher switching accuracy among older children ($p = 0.02$), but the association was not observed in younger children (see **Figure 1**).

DISCUSSION

The current study was among the first large-sample investigations designed to better understand how CRF and age were associated with three aspects of executive function by using the 2-back task, the Flanker task, and the Local-Global task. The primary results revealed that CRF and age were positively associated with the performance of the 2-back task and the Flanker task. The interactions of CRF and age on the Local-Global task indicated the positive association between CRF and the performance of the switching condition in older preadolescents.

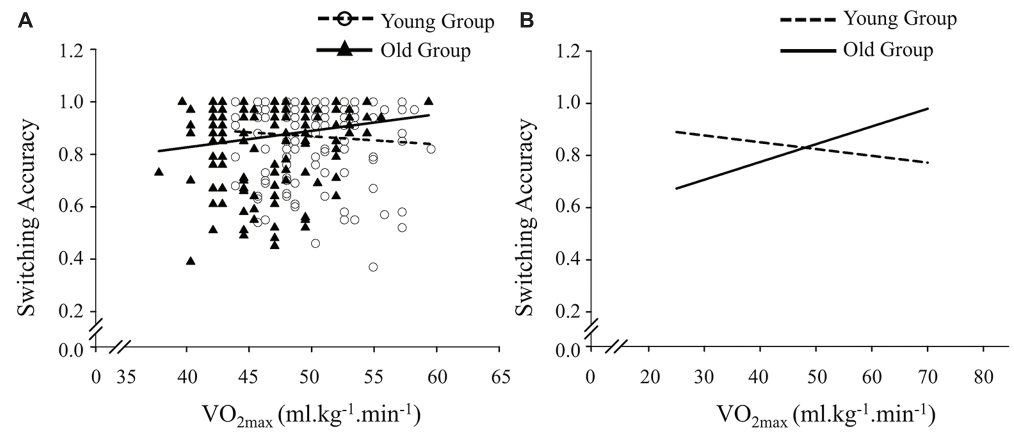

FIGURE 1 | Scatterplots of the relationships between cardiorespiratory fitness (i.e., VO_{2max}) and switching accuracy of the Local-Global task. **(A)** Raw data and **(B)** data that adjusted within the regression model.

The findings of CRF being positively associated with higher accuracy in the 2-back task suggest that CRF is linked to working memory. Similar findings were also observed in CRF and working memory assessed by different tasks. Scudder et al. (2014) reported that young children who completed more laps were associated with superior working memory (response accuracy and working memory *d*' scores) assessed using the field-based CRF (PACER test) and the spatial *N*-back paradigm. Laboratory-based assessed CRF (VO_{2max}) has also revealed increased response accuracy and working memory *d*' scores *via N*-back task (Drollette et al., 2016; Kao et al., 2017b). The subsequent 3-year longitudinal study further indicated that the positive correlations between increased CRF and enhanced working memory performance (the 2-back condition of the *N*-back task) were more potent at the more cognitively demanding task condition (Scudder et al., 2016). These studies that utilized different approaches to assess CRF and working memory provide a strong argument for the positive linkage between CRF and working memory from convergent perspectives.

The current study observed the association between CRF and inhibitory control aspect of executive function, regardless of the conditions of the Flanker task, being broadly consonant with prior research. In other words, children who completed a higher number of PACER laps were associated with better performance (i.e., shorter response times) in both congruent and incongruent conditions of the Flanker task relative to those completed few laps, suggesting a generally beneficial effect of CRF on inhibitory control among preadolescents (Scudder et al., 2014, 2016; Kao et al., 2017a; Raine et al., 2018; Westfall et al., 2018). Similar results showing an association between CRF levels and cognitive performance, regardless of the demands placed on executive function (including the differing demands of the congruent and incongruent conditions of the Flanker task), were also observed in elementary school children (Hillman et al., 2014; Scudder et al., 2014, 2016) and adolescents (Westfall et al., 2018). Collectively, the general improvements associated with CRF and inhibitory control-related tasks could be observed from preadolescent to adolescent children.

Along with CRF, our study also observed positive associations with age and working memory as well as age and inhibitory control, which are in line with prior developmental literature that the performance of working memory and inhibitory control continuously improved throughout childhood until the age of 15 years. The older children demonstrated superior working memory performance assessed by the *N*-back task and inhibitory control performance assessed by the Flanker task and evidenced by shorter response times or higher response accuracy (Best and Miller, 2010). Notably, a shorter response time without any of the negative impacts on the response accuracy for the Older Group suggests that age-induced increased performance does not result from the speed-accuracy trade off. In line with studies associated with CRF, these studies reflect a strong linkage between age and two types of executive function: working memory and inhibitory control. Our study has extended the existing knowledge by examining CRF and age simultaneously in preadolescent children.

The current findings have further demonstrated that age might moderate the correlation between CRF and shifting performance. Specifically, the positive relationship was only evident for older but not for younger preadolescent children during the more difficult parts of the task that require the upregulation of shifting ability. Our results have extended the previous research showing that 6–12-year-old children with a higher CRF were associated with shorter response times during the switching condition of the shifting paradigm (Ishihara et al., 2018) and have demonstrated that age might modulate the effects of CRF on shifting. The improvement of shifting ability (e.g., decreasing switching cost) usually continues into early adolescence following the inhibition and working memory processes (Huizinga et al., 2006; Best and Miller, 2010). A positive correlation between CRF levels in older adults and the performance of the task-switching paradigm (higher response accuracy for repeated and switching trials), which was mediated by the caudate nucleus volumes at the dorsal region (Verstynen et al., 2012), was observed. Thus, it is plausible that the limited beneficial effects of CRF on younger preadolescents were due to their lower levels of cortical maturation. Collectively, current findings have filled the gap of a lack of data concerning shifting and CRF in different ages of preadolescents (Verburgh et al., 2014) and have provided direct evidence of the performances on field tests of CRF and the shifting aspect of executive function.

To the best of our knowledge, this study was the first to investigate the CRF and working memory, inhibitory control, and shifting aspects of executive function simultaneously in a large sample of preadolescents from two age groups, thus making it possible to explore the associations between CRF, age, and more than one aspect of executive function in preadolescents. Despite the exciting findings from the current study, several limitations should be acknowledged. First, the CRF in the current study was assessed through the field-based PACER method. Although the maximum oxygen consumption (VO_{2max}) has been considered as the gold standard for CRF assessment, the requirement of sophisticated equipment and the relatively high cost limited the application in the settings such as school and populational-based studies (Castro-Pinero et al., 2010). Second, the order of conducting the cognitive tasks was not counterbalanced across groups and individuals, and the fixed order might influence the results of current findings. Lastly, since the current study was cross-sectional, the directions of the associations between CRF levels, ages, and cognitive performance could not be determined. Future research would benefit from utilizing longitudinal observational or randomized control interventional approaches so that the influence of the changes in CRF on various aspects of executive function among preadolescent children over time could be elucidated, and the associated causality could be more clearly established.

In conclusion, children with higher levels of CRF or older children were generally associated with better working memory, inhibitory control, and shifting aspects of executive function. Notably, the interaction of CRF and age on shifting further suggests the role of developed cortical maturation in the relationship between CRF and executive function.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

Conceptualization: ZZ, C-HC, JA, FR, LL, and Y-KC. Methodology: LL, FR, and Y-KC. Formal analysis: ZZ, LL, and Y-KC. Investigation: ZZ, JA, and LL. Data curation: ZZ, FR, and JA. Writing – original draft preparation: ZZ, C-HC, JA, and Y-KC. Writing – review and editing: all authors. Visualization: ZZ and JA.

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ORIGINAL RESEARCH
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Acute High-Intensity Interval Exercise Improves Inhibitory Control Among Young Adult Males With Obesity

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Objective: The aim of the present study was to examine the influence of acute high-intensity interval exercise (HIIE) on neural and behavioral measures of inhibitory control in young male adults with obesity.

Design: The present study employed a within-subjects design.

Methods: Sixteen male adults with obesity [body mass index (BMI) > 28 kg/m^2] were recruited. Reaction time and response accuracy of the Flanker task as well as P3 and late positive potential (LPP) components of the event-related potential (ERP) were measured following HIIE and a sedentary control, in counterbalanced order. The HIIE session consisted of 30 min of stationary cycle exercise (5-min warm-up, 20-min HIIE, and a 5-min cool-down), whereas the control condition consisted of a time and attention-matched sedentary resting session.

Results: Faster response times were observed following HIIE regardless of Flanker task condition. Faster and more accurate responses were also observed for congruent relative to incongruent conditions across both sessions. Relative to the neuroelectric data, acute HIIE resulted in increased LPP amplitude but did not affect P3 amplitude.

Conclusion: Collectively, a single bout of HIIE has a general beneficial effect on basic information processing and inhibitory control among young adult males with obesity. Acute HIIE was found to impact LPP amplitude, but not the P3, which may suggest a modulation in the ability to successfully maintain attention and filter irrelevant information to achieve successful cognitive inhibition. Future research is warranted to extend these findings to a larger sample size that includes both genders, other cognitive functions, and a comparison of different modes of exercise.

Keywords: HIIE, executive function, inhibitory control, obesity, P3, LPP

INTRODUCTION

Obesity is a global public health concern that is associated with an increased risk of adverse health conditions including cardiovascular disease and diabetes (Ng et al., 2014) as well as impaired cognition, including executive function, attention, decision making, and memory (Smith et al., 2011; Prickett et al., 2015; Yang et al., 2018). Obesity has also been associated with impairments in inhibitory control. Inhibitory control, a core domain of the executive function, reflects as the ability to suppress inappropriate actions or override the processing of task-irrelevant or distracting information (Bari and Robbins, 2013). Inhibitory control is supported and regulated by multiple bidirectional neural connections, and has been shown to play a crucial role in the ability to inhibit excessive eating behaviors to maintain a healthy weight (Hwang et al., 2010). For instance, individuals with obesity performed worse (slower and less accurately) across several inhibitory control tasks (e.g., Flanker and Stroop inhibitory control tasks), suggesting an impaired ability to override interference information among individuals with obesity relative to their normal-weight counterparts (Kamijo et al., 2012; Gameiro et al., 2017). A recent meta-analysis also reported a moderate inverse effect size for inhibitory control deficits among overweight and obese individuals (Yang et al., 2018). Atrophy of prefrontal cortical regions implicated in cognitive control has been found in individuals with obesity, providing evidence of obesity-impaired cognitive inhibition through both structural and functional brain imaging data (García-García et al., 2015).

Robust and consistent evidence has shown that acute exercise that represents a single bout of exercise elicits beneficial effects on cognitive function (Etnier et al., 1997; Ferris et al., 2007; Chang et al., 2012b; Etnier and Chang, 2019; Wilke et al., 2019) and the beneficial effects from acute exercise have also extended to inhibitory cognitive control (Themanson and Hillman, 2006; Drollette et al., 2014; Chu et al., 2015; Hsieh et al., 2018). However, studies that have investigated acute exercise and inhibitory control have almost exclusively relied on traditional aerobic or resistance modes of exercise (Harveson et al., 2016; Hsieh et al., 2016; Ludyga et al., 2017) and the acute effect of other modes of exercise, particularly those that are engaged in by an increasing number of adults, require consideration to advance our knowledge regarding both efficacy and mechanisms of action (Chang et al., 2019).

High-Intensity Interval Training (HIIT) is a popular and emerging exercise mode that has been shown to elicit beneficial health effects in an efficient manner compared to more long-duration continuous exercise. HIIT generally involves repeated bouts of short to moderate duration high-intensity interval exercise (HIIE) with a larger than anaerobic threshold intensity and interspersed with recovery periods or light exercise (Laursen and Jenkins, 2002; Weston et al., 2014). The HIIE has been linked to improved physical fitness including cardiorespiratory fitness (O'Donovan et al., 2005), skeletal muscle metabolism (Rognmo et al., 2004), and body composition in adults with obesity (Wewege et al., 2017). HIIE has also been shown to positively impact cognitive function. For example, adults exhibited faster overall reaction times and improved accuracy in the Flanker task following 9 min of HIIE compared to a control condition (Kao et al., 2017) and adult males have demonstrated an improvement in inhibitory control (i.e., Stroop test performance) during the post-exercise recovery period after a 28 min bout of cycling HIIE (Tsukamoto et al., 2016). Yet, these studies have only been targets on healthy adults with normal weight, and whether the positive effects of HIIE on cognitive function extend to an adult population with obesity remains unclear. Though only a few studies have examined the effects of exercise on cognition in obese populations, Russo et al. (2017) found that aerobic exercise may improve cognition in obese adults. Previous studies have also demonstrated that HIIE may be more effective than continuous aerobic exercise at improving cognition among normal-weight adults (Tsukamoto et al., 2016; Kao et al., 2017, 2018); therefore, it is possible that HIIE may be an effective mode of exercise for improving cognition in individuals with obesity. One previous study was conducted to examine the impact of HIIE on cognition in obese adults, and showed an improvement in cognitive function, particularly in inhibitory control (Stroop test) after HIIE (Drigny et al., 2014). However, this study was a long-term intervention with HIIE that included only six participants and lacked a control group. Additionally, Quintero et al. (2018) conducted an acute HIIE study on cognitive function in overweight male adults and found positive effects on cognitive inhibition. However, the sample size of their study was relatively small (six participants in HIIE group) and the population was overweight rather than obese. Therefore, the effects of acute HIIE on cognitive function among obese adults is still preliminary, and further investigation is warranted.

Event-related brain potentials (ERPs) from the ongoing electroencephalographam (EEG) represents a sensitive, high temporal resolution of underlying neurocognitive mechanisms between the presentation of a stimulus to beyond response execution processes, and have been commonly utilized to examine the relation between acute exercise and inhibition aspect of executive function (Kamijo et al., 2007; Chu et al., 2015; Wang et al., 2015; Kao et al., 2017). Notably, the majority of studies to date have focused on the P3 (P300 or P3b) component of the ERP, and the acute exercise effect on other components (e.g., late positive potential, LPP) require further examination. The LPP is an ERP component with a more extended latency, which reflects high-order attention processes (Schupp et al., 2003; Carbine et al., 2018) and the influence of cognitive conflict on the later phase of processing (Ligeza and Wyczesany, 2017). Increased LPP amplitude to a stimulus is associated with the increased conscious allocation of attention (Schupp et al., 2003; Carbine et al., 2018) and cognitive control (Watson and Garvey, 2013; Carbine et al., 2018), reflecting a linkage between LPP and inhibitory control.

There has been limited research conducted to examine the influence of HIIE on cognitive function among normal weight adults (Tsukamoto et al., 2016; Kao et al., 2017, 2018) or among overweight or obese adults (Drigny et al., 2014; Quintero et al., 2018). Therefore, it remains important to investigate the effects of acute HIIE on cognitive function among obese adults. It is also unknown how HIIE may affect cognitive function among obese individuals – that is, the precise underlying mechanisms involved. Therefore, the aim of current study was to examine the effects of acute HIIE on cognitive function in young adults with obesity. Specifically, the inhibitory control domain of executive function was assessed via both behavioral and electrophysiological measures using the P3 and LPP components following HIIE. It was hypothesized that an acute HIIE session would facilitate inhibitory control performance among young adults with obesity, and this improvement would be demonstrated by increased P3 and LPP component amplitudes.

MATERIALS AND METHODS

Participants

Sixteen male adults between the age of 18 and 35 years were recruited from the Fengxian district of Shanghai. Eligible participants were screened by the following requirements: (a) obesity status: body mass index (BMI) > 28 kg/m^2 (the value represents the cutoff point obesity on the Asia weight categories); (b) right-handed dominance, (c) no history or presence of endocrine and cardiovascular diseases; (d) no history or presence of neurological disorders or head injury with loss of consciousness; (e) no current use of medication that could affect blood glucose and insulin levels, or any weight loss supplement; (f) "No" answer in any questions of Physical Activity Readiness Questionnaire; and (g) normal or corrected-to-normal vision. All participants provided written informed consent in accordance with the Institutional Review Board at the Shanghai University of Sport (#102772019RT005). The data of the demographic characteristics are provided in **Table 1**.

Cardiovascular Fitness Assessment

The YMCA submaximal ergometer exercise test (MONARK 894E, Sweden) was conducted to assess participants' cardiorespiratory fitness (i.e., maximum oxygen consumption, VO_{2max}). The protocol comprises several consecutive 3-min stages. During the test, a Polar heart rate (HR) monitor was continuously worn to monitor HRs. In the first stage, participants were instructed to cycle at a cadence of 50 rpm at a workload of 25 W (150 kg/min, 0.5 kp). The workloads of the following stages were calibrated according to the HRs of the last 15–30 s (i.e., the steady-state HRs) of the first stage. For instance, the subsequent workloads of the second and third stages were set to 100 W (600 kg/min, 2 kp) and 125 W (750 kg/min, 2.5 kp), respectively, if participant's HRs were lower than 86 bpm. If the steady-state HRs were between 86 and 100 bpm, the workloads of the second and third stages were set to 75 W (450 kg/min, 1.5 kp) and 100 W (600 kg/min, 2 kp), respectively. Lastly, if HR was higher than 100 bpm, the second and third stages were set to 50 W (300 kg/min, 1 kp) and 75 W (450 kg/min, 1.5 kp), respectively. If HR did not achieve steady state in each stage, an additional 1-min cycling was added. The original 6–20 rating of perceived exertion (RPE) (Borg, 1982) was documented every 2 min throughout the test.

TABLE 1 | Demographic characteristics of study participants (means ± SD).

Age (years)	24.50 ± 5.09
Height (m)	1.77 ± 0.06
Weight (kg)	108.11 ± 16.72
BMI (kg/m^2)	34.34 ± 4.39
Digital span	
Forward	14.44 ± 2.28
Backward	9.69 ± 3.63
Education level	
High school	2
College	11
Post-Graduate	2
VO_{2peak} (ml/kg/min)	29.74 ± 12.38
Basal metabolic rate (kJ/m^2/h)	2072.29 ± 191.84
DEBQ	
Restrained eating	3.07 ± 0.37
External eating	3.37 ± 0.62
Emotional eating	2.16 ± 0.74

BMI, body mass index; DEBQ, Dutch Eating Behavior Questionnaire.

Flanker Task

The computerized Flanker task was utilized to assess several aspects of cognitive function (e.g., basic information processing and the inhibitory control aspect of the executive function) implemented on E-Prime software (version 2.0, Psychological Software Tools, Pittsburgh, PA, United States). Each stimulus was composed of five arrows (i.e., one central target and four surrounding flankers) and was presented on the center of the 27-inch LCD screen with a gray background at a distance of 90 cm from participants. The direction of the center target was either the same as the flankers (e.g., →→→→→ or ←←←←←; the congruent condition) or opposite to the flankers (e.g., →→←→→ or ←←→←←; the incongruent condition). A black cross was flashed for 500 ms as a cue to signal the beginning of the trial, followed by the presentation of stimuli for 1000 ms. Once a response was made, a blank intertrial interval with a various time interval (i.e., 600–800 ms) was presented. Participants were asked to put their right index fingers on the number "5" key but not press it, then press the key on the keyboard (number "4" key for left directions and number "6" key for the right directions of the central target, respectively) as fast and accurate as possible. After the key was pressed, the participants were instructed to place their right index fingers back to the "5" key to await the next stimuli. Incorrect responses, responses made beyond 1000 ms after the stimulus onset, or reaction time more than ±3 standard deviations (SD) of each participant's mean reaction time, were discarded from the further analysis. The task contained one practice block and two formal blocks of trials. In the practice block, there were 12 trials with an equal number of congruent and incongruent trial conditions. Participants were required to pass the practice block of trials with an accuracy rate higher than 80%. Each of the formal blocks contained 100 trials, and each of the four stimulus trial types occupied 1/4 of the whole block of trials. The reaction time of accepted response and accuracy for the congruent and incongruent conditions were recorded as the indices of behavioral performance.

Electrophysiological Recording and Analysis

The activity of continuous EEG was recorded from a 64 Ag/AgCl cap with electrodes located at the standard International 10–20 positions using a 1000 Hz sampling rate (Brain Products GmbH, Munich, Germany) throughout the Flanker task. The reference electrode was placed over FCz, and the ground electrode was the AFz. The vertical electrooculogram (VEOG) and the horizontal electrooculogram (HEOG) were recorded through the electrodes placed below the left eye, and the electrodes at lateral-orbitally of the right eye, respectively. All electrodes impedances were kept below 10 kΩ .

All EEG offline processing was conducted using Brain Vision Analyzer 2. The offline EEG data were initially re-referenced according to the average of the left and right mastoids, and the ocular correction was performed (Gratton et al., 1983). Artifact rejection was based on the exclusion of all epochs that exceeded ±100 V. The baseline was corrected (−200 to 0 ms pre-stimulus onset). The continuous EEG data were epoched into 1700-ms time windows (from 200 ms before to 1500 ms after the stimulus onset) for correct trials and then filtered with an IIR filter (low cutoff: 0.1 Hz, high cutoff: 30 Hz, slope: 48 dB/oct). The mean number of analyzable segments of congruent and incongruent conditions were 94.41 ± 7.67 (range 70–100) and 90.84 ± 9.63 (range 60–100), respectively. P3 and LPP component amplitudes were quantified as the area-averaged amplitude within 300–400 ms and 600–1100 ms after the stimulus onset from the Fz electrode (Luijten et al., 2016; Kao et al., 2018), respectively, for both the congruent and incongruent conditions.

Experimental Procedure

Participants were invited to the laboratory on two separate occasions, with the HIIE and control sessions performed in a randomized order across participants. The written informed consent, the physical activity readiness questionnaire (Thomas et al., 1992), and a demographics survey were completed in the participant's first visit. Intelligence indexed by the Digit Span Forward and Backward tests from the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) (Wechsler, 1997) and socioeconomic status were also measured. Weight and height were measured using an electrical scale (Yaohua Weighing System Co., Shanghai, China) and a wall-mounted stadiometer (TANITA, Tokyo, Japan), respectively. The index of BMI was calculated using the standard formula as weight (kg)/height $(m)^2$. Participants also completed the Dutch Eating Behavior Questionnaire (DEBQ), which is used to examine eating styles and contains 33 items to specifically explore restrained eating, external eating, and emotional eating (Van Strien et al., 1986). Previous research has demonstrated strong internal consistency of this measure in both genders and among both obese and normal-weight individuals (Cronbach's alphas > 0.79) (Wardle, 1987).

For the experimental sessions (i.e., HIIE and control sessions), the HIIE session lasted approximately 30 min and involved 5 min of warm-up, a 10 × 1 min of 80–90% maximal HR (HR_{max}) interspersed by 1 min of 50–65% HR_{max} active relax (for a total

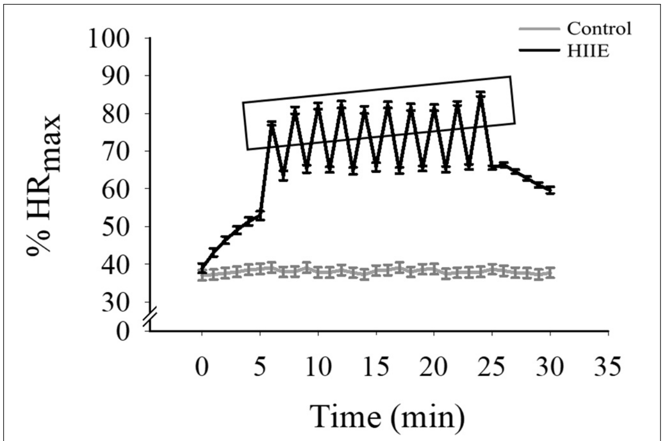

FIGURE 1 | The alteration of the percentage of HR_{max} (%HR_{max}) through both experimental conditions. The *x*-axis (1 min and 30 min) indicates %HR_{max} of the start and end of each condition, which is shown on the *y*-axis. The rectangle indicates %HR_{max} immediately following each HIIE interval.

for 20 min), and 5 min of cool-down. The exercise was conducted via stationary cycle exercise because of biomechanical loads and knee safety concerns that may present among obese adults (Salih and Sutton, 2013). HRs and RPE were recorded every 1 min during the 20-min formal HIIE exercise bout. In the control session, participants sat silently with their eyes opened for 30 min, and HR was recorded throughout (**Figure 1**).

Within 15 min following the HIIE or control session, participants were seated comfortably in a chair while EEG was prepped. Then, the cognitive task was performed, and EEG was recorded throughout the task period. The cognitive task included three blocks, with one practice and two formal blocks. The total duration for each experimental session was roughly 50 min, and participants were debriefed following the final experimental session.

Statistical Analysis

The study is a within-subject design, with session and stimuli conditions as within-subject factors. For the behavioral data, a 2 (session: HIIE vs. control) × 2 (congruency: congruent vs. incongruent) repeated-measures analysis of variance (ANOVA) was conducted for reaction time and response accuracy, respectively. For the ERP data, a 2 (session) × 2 (congruency) ANOVA was separately conducted for P3 and LPP component amplitudes at site Fz. Pairwise comparisons with Bonferroni adjustments were conducted as follow-up analyses. All statistical values were conducted with $\alpha = 0.05$, where the Greenhouse–Geisser corrections and partial eta-squared (η_p^2) values are reported for significant statistics were observed.

RESULTS

Behavioral Performance

The ANOVA analysis of reaction time revealed a significant main effect of session [$F(1,15) = 7.61$, $p < 0.05$, $\eta_p^2 = 0.34$],

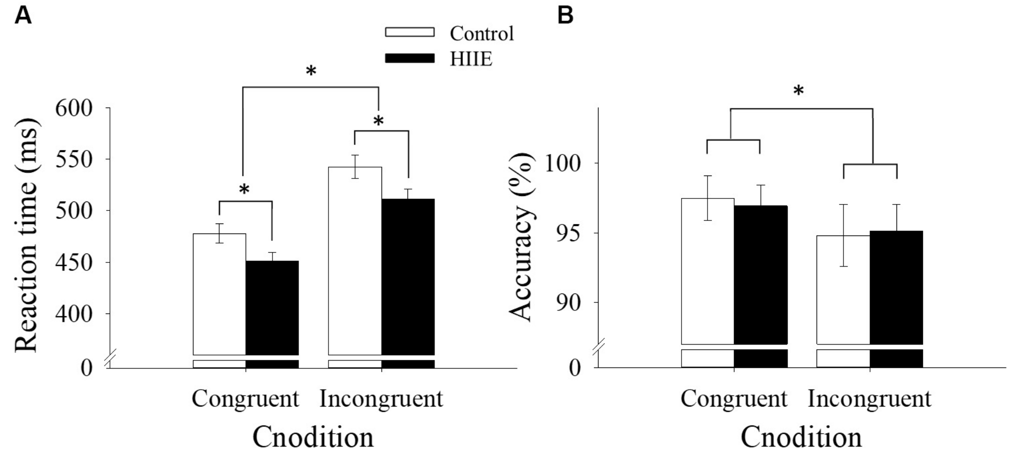

FIGURE 2 | Behavioral reaction time **(A)** and accuracy data **(B)** for the Flanker task by session and congruency. $*p < 0.05$.

with faster reaction time observed following the HIIE condition (481.28 ± 8.69 ms) compared with the control condition (510.29 ± 10.10 ms). The analysis also revealed a significant main effect of congruency [$F(1,15) = 266.44$, $p < 0.001$, $\eta_p^2 = 0.95$], with faster reaction time for congruent (464.69 ± 7.29 ms) compared with incongruent (526.87 ± 8.73 ms) trials. There was no significant interaction between session and congruency ($p > 0.05$). The behavioral reaction time data for the Flanker task are shown in **Figure 2A**.

The analysis of response accuracy revealed a significant main effect of congruency [$F(1,15) = 14.64$, $p < 0.01$, $\eta_p^2 = 0.49$], with more accurate responses observed for congruent (97.20 ± 1.5%) than incongruent (95.00 ± 2.00%) trials. However, no significant differences in response accuracy were observed between HIIE and the control session ($p > 0.05$), nor was there a significant interaction between session and congruency ($p > 0.05$). Response accuracy data are shown in **Figure 2B**.

EEG Data

Figure 3 illustrates the mean stimulus-locked ERP waveform showing P3 and LPP component amplitudes for each session and stimulus condition.

P3 Component Amplitude

Analysis of P3 amplitude revealed no significant main effect for session or congruency ($ps > 0.05$). There was also no interaction between the experimental session and congruency for P3 amplitude ($p > 0.05$).

LPP Component Amplitude

Analysis of LPP component amplitude revealed a significant main effect of session [$F(1,15) = 6.91$, $p < 0.05$, $\eta_p^2 = 0.32$], with larger LPP amplitude observed following the HIIE (13.73 ± 1.86 μV) compared with the control condition (9.64 ± 1.43 μV) at Fz. There is also a significant main effect of congruency [$F(1,15) = 6.69$, $p < 0.05$, $\eta_p^2 = 0.31$], with larger LPP amplitude for congruent (12.27 ± 1.56 μV) compared with incongruent (11.10 ± 1.40 μV) task conditions. No significant interaction between session and congruency was found ($ps > 0.05$). In addition to the grand averaged ERPs, topographic scalp distribution of neuroelectric activity within the time frame of the LPP at site Fz has been shown in **Figure 3**.

DISCUSSION

The study examines the effect of an increasing popular mode of exercise, acute HIIE, on both behavioral and neural indices of inhibition control. Along with the few studies that have been conducted to determine the effects of a single bout of HIIE on inhibitory control, this is the first to examine the influence of this form of exercise on the P3 wave and LPP component among young adult males with obesity. The findings indicate that acute HIIE elicits faster reaction times, but no change in response accuracy, regardless of Flanker task congruency compared to a no-exercise control session. Additionally, while no acute exercise-related enhancements were observed for P3 amplitude, acute HIIE increased LPP component amplitude regardless of Flanker task conditions. Overall, these findings support previous research demonstrating that a single bout of moderate-intensity aerobic exercise increases inhibitory cognitive control (Pontifex et al., 2019) and extends these beneficial findings to HIIE and to young adult males with obesity.

Previous studies have shown that a single bout of HIIE improves inhibitory control performance among normal-weight adults (Alves et al., 2014; Tsukamoto et al., 2016; Kao et al., 2017, 2018) and the present study exhibited faster reaction time following acute HIIE that extends to male adults with obesity. The previous study also indicated decreased flanker task reaction time (Kamijo et al., 2007; Kao et al., 2017) and decreased Stroop reaction time following similar exercise protocols (Alves et al., 2014; Tsukamoto et al., 2016). Given that both of these two tasks are associated with the inhibitory domain of executive function or cognitive control (Harnishfeger and Bjorklund, 1993), the more efficient reaction times observed in these tasks suggest that acute HIIE enhances response speed (Kao et al., 2017) and improved

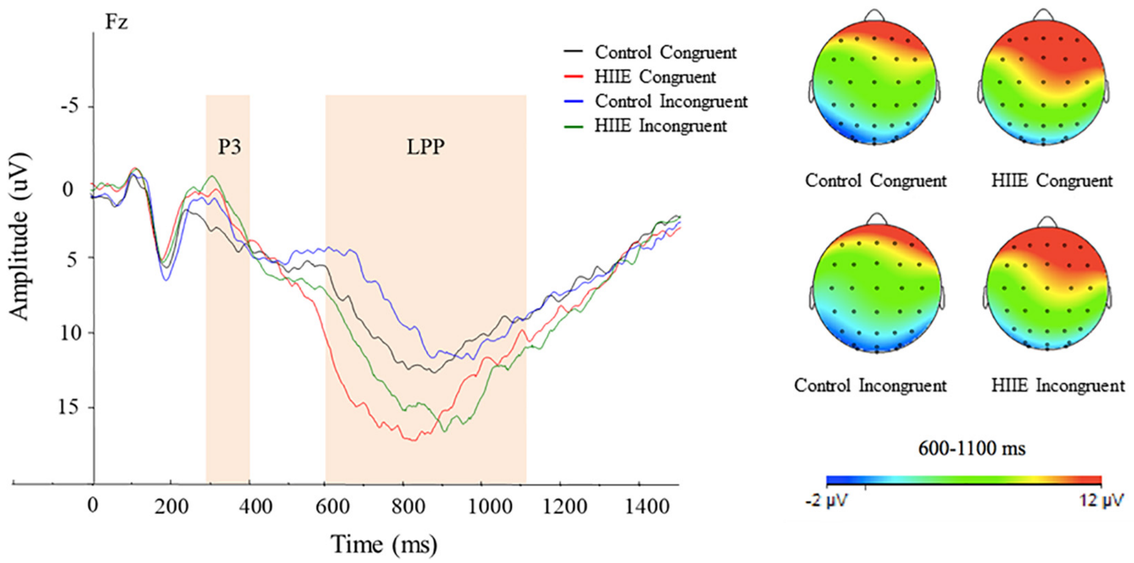

FIGURE 3 | Grand-mean stimulus-locked ERP waveforms for each session and task condition. Stimulus-locked waveforms are shown for both congruency conditions at the midline electrode sites at Fz. Topographic maps of scalp neuroelectric activity for each session and task condition for LPP amplitude (right). The average area of P3 and LPP component amplitudes are shown in shaded regions. LPP component revealed larger amplitude observed following the HIIE (green and red) compared with the control condition (black and blue) at the Fz site. Topographic scalp distribution of the LPP revealed larger activation following the HIIE condition compared with the control condition at Fz regardless of congruency condition.

efficiency in cognitive inhibition (Harnishfeger and Bjorklund, 1993; Kamijo et al., 2012), reflecting a facilitation in inhibitory control following acute HIIE. That this effect is observed in young males with obesity is also provocative since the exercise stimulus is likely to be more difficult relative to normal-weight counterparts performing similar overall workloads.

Behavioral performance of reaction time and accuracy was impaired in the more difficult incongruent relative to congruent task condition of the Flanker task, an effect that is consistently found in the literature (Alderman et al., 2016). These results have often been interpreted as a "conflict effect," suggesting an increase in the task difficulty during incongruent task trials (Eriksen and Eriksen, 1974). In the incongruent task condition, a greater amount of interference control is involved, resulting in response delays, which is due to the fact that flanking stimuli provoked by the activation of the incorrect response compete with the correct response produced by the central target stimulus (Spencer and Coles, 1999; Larson et al., 2014). Notably, the improvement in cognition observed following the acute HIIE not only occurred for congruent but also for incongruent task conditions. Given that the congruent condition reflects relative basic information processing, whereas the incongruent condition reflects high-order inhibition, our results suggest that acute HIIE may have an overall general facilitating effect on cognitive function. These results are somewhat in contrast with studies that have demonstrated a selective improvement (e.g., faster cognitive processing speed) in the incongruent condition but not in congruent or neutral conditions after acute HIIE (Kamijo et al., 2007; Kao et al., 2017). Drollette et al. (2014) found that participants with lower inhibitory capacity may be among those who benefit the most from single bouts of exercise. Therefore, it is possible that the obese individuals from this study have a less flexible cognitive function, particularly within the domain of inhibitory control, relative to their normal-weight counterparts, and acute HIIE may generally enhance both their basic cognitive functioning and high-order cognitive functions such as inhibitory control. This speculation of individual differences in acute exercise–cognition relationship warrants future investigation, particularly given the rise of obesity in nearly all developed countries around the world.

In opposition to our hypothesis, we did not observe an effect of HIIE on P3 amplitude, suggesting that the allocation of attentional resources or cognitive processes that may be indexed by the P3 is not influenced following HIIE among young obese male adults. These results contrast with many previously published studies that have observed an increased P3 amplitude following the acute exercise (Drollette et al., 2014; Chu et al., 2015; Hsieh et al., 2018); yet, it should be noted that these increased P3 amplitudes following acute exercise have only been shown following continuous moderate-intensity aerobic exercise. Indeed, Kao et al. (2018) led a recent study to investigate the short-term neurocognitive effects of acute HIIE and did not find any significant change in P3 component amplitude compared to a sedentary control condition, findings similar to those shown in this study. Collectively, the findings from these two studies suggest that the type or mode of exercise might be a significant moderator of the acute exercise-related enhancement in cognitive function. In addition, the duration of exercise might also be a critical modulator of any acute exercise effects. Kao et al. (2017) found a decrease in P3 amplitude and latency following a 9-min session of HIIE compared to seated rest. They reasoned that such decreases in P3 amplitude following HIIE could be regarded as greater neural efficiency because of less recruitment of neural resources accompanied by improved inhibitory control (Voss et al., 2011; Malinowski, 2013; Kao et al., 2017). However, the results were in contrast with their study in 2018 (Kao et al., 2018), which found no change in P3 amplitude after a 16-min session of acute HIIE, and thus one consideration for the difference may have been due to the duration of the exercise. Given that the exercise duration used in this study was similar to that used in the Kao et al. (2018) study, we expect that exercise duration might have an important influence on P3 component amplitude, particularly when incorporating HIIE protocols. Specifically, HIIE with longer durations might lead to limited effects on P3 amplitude, and the extent to which this influences overall behavioral performance remains to be examined. Lastly, previous studies have mostly examined normal-weight individuals and very few studies to date have focused on the acute HIIE effects on behavioral and neural exponents of inhibitory control among obese adults; therefore, the results from this study relative to behavioral performance outcomes of the P3 may be specific to this population.

Our findings that HIIE improved LPP amplitude is novel for several reasons. LPP reflects higher-order attentional processes (Schupp et al., 2003; Carbine et al., 2018) and the influence of cognitive conflict on the late phase of processing (Ligeza and Wyczesany, 2017). In addition, although we did not use an emotional stimulus in this study, LPP amplitude has also been interpreted as a global inhibition of activity within the visual cortex, reflecting a more adaptive emotional processing (Brown et al., 2012). Our findings demonstrate that following acute HIIE, LPP amplitude increases, suggesting a modulation in the ability to successfully maintain attention and filter irrelevant information to achieve successful cognitive inhibition involved in the Flanker task.

The major strengths of the study include the investigations of the acute HIIE effects on multiple aspects of cognitive function as well as its neuroelectric response in obese individuals; however, potential limitations should be proposed. Our study only included obese male adults in order to avoid the potential moderating role of sex (males vs. females). Along with the relatively small sample size, these findings should not be broadly generalized and future studies employing larger sample size with a specified recruitment of both genders are recommended to further examine the influence of HIIE on select aspects of cognitive function. Additionally, while inhibitory control is a core component of executive function, other distinguishable components including shifting and updating (Miyake et al., 2000) as well as planning (Chang et al., 2012a) should be studied. These distinct components might be differentially influenced by various features of acute HIIE and should be examined to provide a more complete picture of acute HIIE-related modulations of executive function. Furthermore, previous studies have indicated the physiological response to HIIE and more traditional forms of aerobic exercise are different for normal-weight adults. However, the effects and brain mechanisms involved in the acute effects of HIIE on cognition in obese individuals were unclear and thus it is recommended for future studies to compare the impact of both HIIE and aerobic exercise among obese individuals. Lastly, further investigation is also warranted to explore the dose–response relationship between acute HIIE and cognitive function, in terms of intensity, duration, and volume, to advance more precise exercise prescription for cognition.

CONCLUSION

Collectively, a single bout of HIIE has a general beneficial effect on basic information processing and inhibitory control among young adult males with obesity. Acute HIIE was shown to impact LPP component amplitude, but not P3 component amplitudes, which may suggest a modulation in the ability to successfully maintain attention and filter irrelevant information to achieve successful cognitive inhibition. Future study is suggested to extend the examination to a larger sample size that includes both genders, other cognitive functions, and a comparison of varied exercise modes.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board at the Shanghai University of Sport (#102772019RT005). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CX, Y-KC, and AL: conceptualization. CX, FM, and JA: methodology. BA, FM, and JA: formal analysis. CX, BA, Y-KC, and AL: investigation. All authors: writing – original draft preparation and review and editing.

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The Mediating Role of Non-reactivity to Mindfulness Training and Cognitive Flexibility: A Randomized Controlled Trial

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Mindfulness training has been shown to have a beneficial effect on cognitive flexibility. However, little is known about the mediators that produce this effect. Cross-sectional studies show that there might be a link between Non-judgment, Non-reactivity and cognitive flexibility. Longitudinal studies examining whether Non-judgment or Non-reactivity mediate the effectiveness of mindfulness training on improving cognitive flexibility are lacking. The present study aims to test the effect of mindfulness training on increasing cognitive flexibility and to test whether this effect is mediated by Non-judgment or Non-reactivity. We conducted a single-blind randomized controlled trial in 54 nonclinical high-stress participants between October 2018 and January 2019. Participants were randomly assigned to a Mindfulness Based Stress Reduction (MBSR) group or a waitlist control group. The experimenters were blind to the group assignment of participants. The MBSR group received 8-weekly sessions (2.5-h per week) and a one-day retreat (6-h), and was required to accomplish a 45-min daily formal practice during the intervention. The waitlist control group did not receive any intervention during the waiting period and received a 2-day (6-h per day) mindfulness training after the post-intervention. The primary outcome was self-report cognitive flexibility and perceived stress administered before and after MBSR. The secondary outcome was self-report mindfulness skills (including Non-reactivity and Non-judgment) measured at pre-treatment, Week 3, Week 6, and post-intervention. For cognitive flexibility, mixed-model repeated-measure ANOVA results showed that there were significant main effects of Time, Group and a significant interaction of Time by Group. Follow-up ANOVA indicated that the MBSR group was associated with greater improvements in cognitive flexibility than the waitlist. Path analysis results showed that the effect of the treatment on cognitive flexibility at post-treatment was fully mediated by Non-reactivity at Week 6. The mediation effects of Non-reactivity at Week 3, and Non-judgment at Week 3 and Week 6 were not significant. Our findings support the efficacy of MBSR on improving cognitive flexibility. Non-reactivity is an important element of the effectiveness of MBSR training on cognitive flexibility.

Keywords: Mindfulness Based Stress Reduction, cognitive flexibility, non-reactivity, mediation, mechanism

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INTRODUCTION

Mindfulness has been defined as attention or awareness to present-moment experiences with acceptance (Baer, 2003; Kabat-Zinn, 2003; Bishop et al., 2004). Importantly, mindfulness is an innate capacity of humans. At the same time, it can be fostered and deepened by mindfulness based interventions (MBIs) (Lindsay and Creswell, 2017), such as the Mindfulness Based Stress Reduction Program (MBSR) (Kabat-Zinn, 1990) and Mindfulness Based Cognitive Therapy (MBCT) (Segal et al., 2012). MBI alleviates psychological distress (e.g., stress, anxiety, mood symptoms) with medium effect sizes compared to waitlist controls (Hedge's gs = 0.41−0.53), and active treatment controls (Hedge's gs = 0.33−0.5) (Hofmann et al., 2010; Khoury et al., 2013). Additionally, preliminary evidence supports that MBI enhances cognitive abilities (e.g., cognitive flexibility, attention, and executive functioning), which might affect social functioning (Lutz et al., 2015; Li et al., 2018; Wielgosz et al., 2019). Some studies suggest that cognitive flexibility promotes effective management of stressful life events, and is associated with good mental health (Kashdan and Rottenberg, 2010; Logue and Gould, 2014).

Cognitive flexibility is conceptualized as the ability to flexibly and adaptively respond to the environments, as opposed to the rigid or automatic thinking style, triggered by prior experience (Hayes et al., 1999; Shapiro et al., 2006; Dennis and Vander Wal, 2010). Lack of cognitive flexibility, or cognitive rigidity, is an important vulnerability for the development and maintenance of psychological distress (Morris and Mansell, 2018). When confronted with difficult life situations, individuals with a rigid thinking style tend to perceive the situation as unchangeable and uncontrollable and tend to engage in rumination, leading to distress in the long term. If individuals see only one solution to a difficult life situation, they might perceive themselves as incapable of problem solving. That might interfere with their long-term goals, which might further increase emotional distress. As part of cognitive behavioral therapy (CBT), psychological distress is alleviated by targeting maladaptive and rigid automatic cognitions with more adaptive cognitions (Derubeis et al., 1991; Chambless and Gillis, 1993). In this context, Dennis and Vander Wal (2010) developed a self-report instrument, the Cognitive Flexibility Inventory (CFI), to measure cognitive flexibility. The CFI consists of two factors, namely the Control factor and the Alternative factor. Items on the Control factor measure the degree to which individuals perceive the difficult life situation as controllable. Items on the Alternative factor denote the extent to which individuals perceive multiple explanations and solutions to the difficult life situation. It seems likely that individuals with flexible and adaptive cognitions experience less psychological distress than those with rigid thinking styles. In fact, a greater level of perceived control has been shown to be associated with higher tendency to adapt coping strategies to different stressful life situations (Cheng and Cheung, 2005). Furthermore, individuals with higher levels of perceived control tend to accommodate with life stressors including economic difficulties, unemployment and care-given burdens (Zautra et al., 2012). Less dichotomous thinking (e.g., If I fail at my work, then I am a failure as a person), was indicative of alleviated perceived stress (Otto et al., 1997; Ford and Shook, 2018). Meanwhile, it is evident that an increase in perceived problem solving capability predicted less perceived stress longitudinally (Otto et al., 1997), suggesting that flexible cognitions contribute to successful management of life event stress.

Mindfulness has long been proposed to be associated with cognitive flexibility. Some researchers have proposed that cognitive flexibility is a component of mindfulness (Bishop et al., 2004; Chanowitz and Langer, 1981; Feldman et al., 2007; Frewen et al., 2008; Moore and Malinowski, 2009). For example, Chanowitz and Langer (1981) defined mindfulness as a consciousness state or a mode of cognitive functions that would allow individuals to get actively involved in reframing the environment. This, in turn, might enable individuals to draw voluntary attention on contextual cues, leading to flexible and adaptive cognitions or behaviors. Bishop et al. (2004) suggested that mindfulness is operationally defined as the self-regulation of attention and orientation to the experience. Being cognitive flexible is considered an important component of self-regulation of attention. However, relatively little is known about the role of cognitive flexibility in mindfulness (Kee and Wang, 2008). Moore (2013) has shown that cognitive flexibility is positively associated with mindfulness and contributed to flow experiences when controlled for mindfulness, suggesting that cognitive flexibility and mindfulness are independent but correlated constructs. Similar to cognitive flexibility, mindfulness was found to be associated with lower levels of perceived stress (Senders et al., 2014; Gustafsson et al., 2015). Shapiro et al. (2006) proposed that mindfulness trainings might facilitate awareness of one's habitual reactions and enable individuals to see the present situation as it is and respond adaptively and flexibly. So far, only one study has shown that MBI improves self-report cognitive flexibility. Shapero et al. (2018) found that for depressed individuals, participants receiving MBCT training reported higher levels of cognitive flexibility than a waitlist group. In sum, mindfulness is positively associated with cognitive flexibility and both of them are associated with lower emotional distress. On top of that, emerging evidence suggests that MBIs might be effective for improving cognitive flexibility.

Although mindfulness has been shown to cultivate adaptive and flexible responses, the mechanism producing this effect requires further exploration. Theoretical models have provided fundamental insights for the underlying mechanism. The mindfulness stress-buffering theory (Creswell and Lindsay, 2014) proposes that acceptance is the main ingredient of mindfulness training on adaptive responses for stress. Acceptance is often defined as openness toward emotion and experience (Campbell-Sills et al., 2006). The ability to accept stressors buffers the habitual appraisals and responses, which in turn facilitates new appraisals and coping strategies. Studies have shown that the association between trait mindfulness with peace of mind was mediated by acceptance (Xu et al., 2015), and the positive link between mindfulness and subjective well-being was significantly mediated by self-acceptance only (Xu et al., 2016). Moreover, accepting pain increased pain endurance and tolerance after training than simply paying attention to the pain without accepting it (Wang et al., 2019).

It has been suggested that accepting an experience might be cultivated by approaches that encourage individuals to fully experience their bodily sensations, emotions, and thoughts without changing or avoiding them (Hayes et al., 1999). However, little is known about the specific mindfulness-based approach that fosters this acceptance attitude. Lindsay and Creswell (2017) proposed that mindfulness training might foster acceptance through non-judgmental (without judging them as good or bad) and non-reactive (without reacting to change them) attitudes toward internal and external experiences. Mindfulness practices emphasize Non-judgment by allowing for any experience arising in our mind, without evaluating them as good or bad. Thus, this process may be presumed to shift habitual stress appraisal sets. Non-reactivity is accomplished through allowing experiences to come and go without reacting in an effort to change them. Non-reactivity is important in explaining the reduction of mood symptoms gained by mindfulness training. After a 3-month training, Non-reactivity predicted more reduction of mood symptoms in a present awareness mindfulness training group as compared to a progressive muscle relaxation training group (Gao et al., 2018). Theoretically, Non-reactivity may buffer the stress reactivity, which in turn would permit the generation of new responses, thus increasing cognitive flexibility (Kuyken et al., 2010; Dajani and Uddin, 2015; Van Der Velden and Roepstorff, 2015). Baer et al. (2012) reported that Non-judgment and Non-reactivity both showed significant improvements from baseline to Week 3 and Week 6 of a mindfulness intervention. Therefore, Week 3 and 6 might be two critical time points when changes in Non-judgment and Non-reactivity during mindfulness training occurs. Although theoretical models make reasonable assumptions, empirical evidence is relatively lacking. Currently, the pathways linking mindfulness training, Non-judgment/Non-reactivity and cognitive flexibility are poorly understood.

The present study aims to examine the effect of MBSR on cognitive flexibility and the mediating role of Non-judgment and Non-reactivity among them. Based on the previous studies, we hypothesized that: (1) Compared to a waitlist control group, the MBSR group will show elevated cognitive flexibility scores at post-intervention; (2) Non-reactivity scores during the intervention will mediate the treatment-induced changes in cognitive flexibility at the post-treatment assessment point; and (3) Non-judgment scores during the intervention will significantly mediate the relationship between intervention group and cognitive flexibility scores at post-intervention.

MATERIALS AND METHODS

Participants

One hundred and two participants were recruited via social media advertisement. The inclusion criteria were: (a) a score on the Chinese Perceived Stress Scales (CPSS; Yang and Huang, 2003) ≥26; (b) having no prior experience with the 8-week MBSR or MBCT protocol; (c) a practice frequency of yoga, meditation, or Tai chi less than 20 min per week in the past six months; (d) absence of severe or unstable physical illness that would prevent one from attending trainings; and (e) a commitment to the group setting (e.g., randomization, no schedule conflicts, no attendance to other MBI or experiments during training). Participants were excluded if they met the DSM-IV-TR criteria (American Psychiatric Association [APA], 1994) for any diagnosis in the past six months. They were excluded if they had any self-injury or suicidal risks, aggression or destructive behaviors. The trial was conducted between October 2018 and January 2019, at the Peking University, Beijing, China.

Procedure

Participants were invited to complete a survey attached to the advertisement. The survey included questions about personal experiences and information (e.g., the prior experience about MBSR or MBCT; the practice frequency of yoga, meditation, or Tai chi; the physical condition), and the CPSS. A study staff member subsequently telephoned to confirm the participant was able to commit to the group setting. Meanwhile, they were invited to attend the Structured Clinical Interview for DSM-IV-TR (First et al., 2002) conducted by a psychiatrist. The CONSORT checklist (Schulz et al., 2010) of this clinical trial is displayed in **Supplementary Material**.

After eligibility assessment, 54 participants were included. To match the gender and age between the MBSR group and waitlist group, a research assistant used a stratified random method to allocate participants. First, the age range was calculated. Then, the potential number of strata was assigned an integer that could be divided by the age range. The optimal number of strata was reached when the gender ratio within each strata became approximately 1:1. In our study, eight was chosen as the final strata number. The randomization was carried out within each strata. The random number sequence from 1 to 100 was generated by Excel. Each participant was allocated to a random number. This random number was divided by 2. If the remainder was 0, the corresponding participant was allocated to the MBSR group. If the remainder was 1, the participant was allocated to the waitlist group.

Twenty-six participants were allocated to the MBSR group, and 28 were allocated to the waitlist group (allocation ratio = 13:14). Group assignment was done by the research assistant. The participants would not be informed of their assignment until they completed the pre-test. Before the pre-test, all participants gave their informed consent. The intervention started on November 2018 and ended on January 2019. The MBSR group received the 8-week (2.5-h per week) sessions and a one-day retreat (a weekend between Week 6 and Week 7), led by two instructors adhering to the MBSR developed by Kabat-Zinn (1990). Meanwhile, participants were asked to practice guided meditation for 45 min daily. The waitlist group was not offered any kind of intervention during the waiting period, but they had access to a 2-day mindfulness training after the post-intervention. Participants were asked to complete the self-report questionnaires at 4 time points based on the timeline of MBSR group: pre-treatment (pre randomization, T1), Week 3 test (T2), Week 6 test (T3), and post-treatment (the week following week

8, T4) (for the flowchart of the participants, see **Figure 1**). The questionnaires were delivered to the participants via an online link before the session. Participants had 40 min for completing the measures. Within the training period, the participants and the instructors were not blind to the group assignment, only the experimenters were blind. Participants who finished all the tests were thanked and received 100 RMB as compensation. Our study protocol was approved by the Association for Ethics and Human and Animal Protection in School of Psychological and Cognitive Sciences, Peking University (No. 2018-10-02).

Measures

The Chinese version (Deng et al., 2011) of the Five Facet Mindfulness Questionnaire (FFMQ; Baer et al., 2008) was used to assess the tendency to be mindful. The FFMQ consists of 39 items with a 5-point Likert rating scale (1 = never or very rarely true, 5 = very often or always true). Its five-factor construct is reliable and valid in English and Chinese settings, which refers to Observing (e.g., "I notice the smells and aromas of things"), Describing (e.g., "I am good at finding words to describe my feelings"), Acting with awareness (e.g., "I find myself doing things without paying attention," reverse coding), Non-reactivity to inner experiences (e.g., "I perceive my feelings and emotions without having to react to them"), and Non-judging of inner experiences (e.g., "I think some of my emotions are bad or inappropriate and I should not feel them," reverse coding). A higher score indicates that one is more mindful in everyday life. If the mediating role of Non-judgment and Non-reactivity is to be verified, their changes have to emerge prior to the changes of outcome variables (Kazdin, 2007). Thus, the FFMQ was evaluated during the MBSR intervention in addition to the pre- and post-treatment. In the present study, the Cronbach's αs of the FFMQ, and the five subscales across 4 time points ranged from 0.84 to 0.93.

The Chinese version (Wang et al., 2016) of the CFI (Dennis and Vander Wal, 2010) was utilized to assess the ability to generate alternative explanations and solutions to difficult situations. The CFI is comprised of 20 items utilizing a 1–5 point Likert rating scale (1 = never, 5 = always). It assesses two aspects of cognitive flexibility: the proneness to perceive difficulties as controllable (e.g., "When I encounter difficult situations, I feel like I am losing control," "I am capable of overcoming the difficulties in life that I face"), and the capability to generate multiple explanations and solutions when confronted with life events and difficulties (e.g., "I consider multiple options before making a decision," "I like to look at difficult situations from many different angles"). The original CFI has good internal consistency (Cronbach's αs = 0.84−0.92), 7-weeks test-retest reliability (r = 0.81) and construct validity for clinical and non-clinical samples (Dennis and Vander Wal, 2010). The Chinese version showed good internal consistency (Cronbach's αs = 0.81) and revealed a two-factor structure, consistent with the original scale. Higher scores indicate more flexibility in cognitive appraisal and problem solving when encountering difficult situations. To examine the efficacy of MBSR on cognitive flexibility, the CFI was administered at pre- and post-treatment. The Standardized Response Mean (SRM) (the mean difference between pre- and post-treatment divided by the standard deviation of the difference), was 0.93, indicating large sensitivity to change (Cohen, 1992). In the present study, the Cronbach's αs of CFI were at 0.75 pre-intervention, and 0.91 at post-intervention.

The CPSS (Cohen et al., 1983; Yang and Huang, 2003) was administered to evaluate the degree to which individuals perceived their situations as uncontrollable, unpredictable, and unresolvable in the past month. The CPSS includes 14 items (e.g., "I feel intense and stressful," "I feel that the problem is constantly accumulating and cannot be solved") with a 5-ponit Likert rating scale (0 = never, 4 = always). It exhibits great internal consistency and construct validity in English and Chinese settings (Cohen et al., 1983; Yang and Huang, 2003). A higher score indicates a higher level of perceived stress. The CPSS was conducted at pre and post-treatment in order to capture the stress reduction effect of MBSR. In the present study, the Cronbach's αs of CPSS were 0.72 at pre-treatment, and 0.86 at post-treatment.

Data Analyses

First, we utilized G*power 3.1 (Faul et al., 2007) to compute the required sample size. Based on a previous study (Shapero et al., 2018), we considered a between-group effect size (η^2) of 0.24 regarding the mindfulness training effect on cognitive flexibility. To obtain power of 0.8 with two measurement points, the total sample size of 50 would be sufficient to detect a significant Group × Time interactions by repeated-measure ANOVAs at $p < 0.05$.

Second, we conducted the missing value analysis with the Statistical Package for Social Sciences (version 17.0 for Windows; SPSS Inc., Chicago, IL, United States). All data were analyzed using multivariate intention-to-treat analyses. For FFMQ, CFI, and CPSS, Little's MCAR (Missing Completely At Random) tests showed that data were missed at random (ps > 0.05). We used the expectation-maximization method suggested by Newgard and Lewis (2015) to impute the missing data. We compared group differences in age, gender, educational years, FFMQ, CFI, and CPSS scores at pre-treatment, using independent sample t-tests for continuous variables, and the chi-square test for the categorical variable. If significant, those would be co-varied in analysis.

Third, effects of MBSR on improvement in perceived stress and cognitive flexibility were examined using mixed-model repeated-measure ANOVAs using SPSS. A series of follow-up ANOVAs or t-tests were conducted following significant main effects and interactions.

Latent growth curve modelings (LGCMs) were conducted to explore the longitudinal trajectories of FFMQ total score and factor scores, and to investigate whether individuals or groups would differ in the initial levels and longitudinal changes in these scores. We estimated two latent factors (intercept and slope) across four waves (T1–T4). The intercept was defined by fixing the four parameters with a loading of 1.0, representing constant initial levels across four waves. The slope was fixed at loadings with 0, 3, 6, 8, representing the time spaces with T1. Group (0 = MBSR, 1 = waitlist) was incorporated as a covariate to test for the treatment effect on trajectories of mindfulness skills.

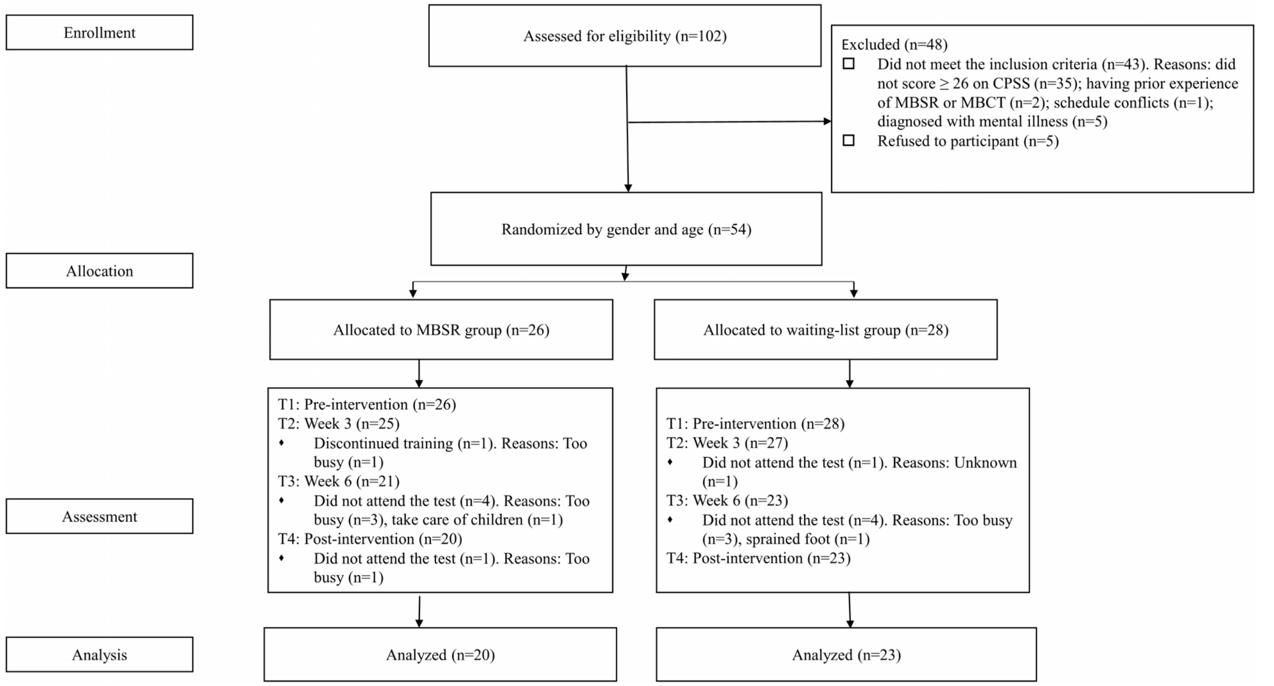

FIGURE 1 | Flow chart of study procedure.

LGCMs were administered using the Lavaan package (Rosseel, 2012) in R. Based on the criteria by Hu and Bentler (1999), CFI > 0.9, RMSEA < 0.08, and SRMR < 0.1 suggest a good fit of the model.

The mediation analyses were performed with Mplus version 5.2 (Muthén and Muthén, 2007). Adopting the method recommended by Baron and Kenny (1986), a mediation effect was determined by calculating the product of path coefficients constituting the indirect effect (e.g., path coefficient of the independent variable to mediator, and path coefficient of mediator to outcome variable) divided by bootstrapped standard error of this product. A bootstrap procedure was used to increase the statistical power (MacKinnon et al., 2002). We ran four separate mediation models to determine whether Non-reactivity at Week 3 or Week 6 and/or Non-judgment at Week 3 or Week 6, mediate the relationship between MBSR training and post-treatment cognitive flexibility. In each model, intervention group, which was transformed into dummy variable (0 = MBSR group, 1 = waitlist group), served as the independent variable. Post-treatment CFI scores served as the outcome variable. Thus, each model comprised of a path ("a" path coefficient) from group (MBSR or waitlist group) to mediator (Non-reactivity at Week 3 or Week 6, Non-judgment at Week 3 or Week 6), a path ("b" path coefficient) from mediator to outcome variable (post-intervention CFI score), and a direct path ("c′" path coefficient) from group to outcome variable controlling for mediator. The indirect effect of MBSR training on cognitive flexibility via the mediator is calculated by "a" multiplied by "b" ("ab" coefficient), the MODEL INDIRECT command was utilized in Mplus 5.2. A mediation effect was marked by a significant *ab* coefficient. In addition, goodness of fit parameters included comparative fit index (CFI), root-mean-square error of approximation (RMSEA), standardized root mean square residual (SRMR). According to the criteria by Hu and Bentler (1999), CFI > 0.9, RMSEA < 0.08, SRMR < 0.1 indicates good fit.

To examine the statistical power, we used Cohen's d to calculate the effect size of t-tests. Cohen (1988) defined a small, medium, and large effect size as 0.2, 0.5, and 0.8. We also used partial η^2 (Cohen's f) to calculate the effect size of the main effects and interactions. A value of η^2 ranging from 0.01 to 0.059 indicates a small, between 0.059 and 0.138 indicates a medium, and values ≥0.138 a large effect size (Cohen, 1988). We adopted the Monte Carlo method to calculate the power of mediation tests (Schoemann et al., 2017). The number of replication was set to 1000. For each replication, 200 times of random draws from the distribution of regression coefficients were used. As suggested by Cohen (1988), for the proportion of a variable explained by another variable, a small, medium, and large effect size was 0.01, 0.09, and 0.25, respectively.

RESULTS

Demographical and Descriptive Data

The two groups were demographically matched and showed no significant difference in age ($t_{(52)} = 0.24$, $p = 0.81$, Cohen's $d = 0.07$, 95% Confidence Interval (CI): −0.48 to 0.61), gender ($X^2_{(52)} = -0.26$, $p = 0.8$), educational years ($t_{(52)} = -0.2$, $p = 0.84$, Cohen's $d = -0.05$, 95% CI: −0.49 to 0.6), or per capita monthly income ($t_{(52)}$ = 0.54, p = 0.6, Cohen's d = 0.15, 95% CI: −0.49 to 0.6). There were no significant group differences in pre-treatment FFMQ ($t_{(52)}$ = −0.82, p = 0.41, Cohen's d = −0.22, 95% CI: −0.77 to 0.32), CFI ($t_{(52)}$ = 1.36, p = 0.18, Cohen's d = 0.37, 95% CI: −0.18 to 0.92) or CPSS ($t_{(52)}$ = −0.67, p = 0.51, Cohen's d = −0.18, 95% CI: −0.73 to 0.37) (see **Table 1**). Thus, no pre-treatment variables were co-varied in the follow-up analysis.

In total, the drop-out rate was 20.37%. Six participants dropped out of the MBSR group (23.08%). Among them, one participant discontinued training at Week 3 because he was too busy, four participants did not attend the Week 6, for the reason of being too busy (n = 3) or taking care of children (n = 1). 1 participant did not complete the post-intervention, reporting being too busy. For the waitlist group, five participants dropped out (17.86%). Among them, one participant did not attend the Week 3 test, reason unknown. Four participants did not complete Week 6 test, for the reasons of being too busy (n = 3) or having a sprained foot (n = 1) (see **Figure 1**).

Trajectory of Change in Mindfulness at Pre-treatment, Week 3, Week 6, and Post-treatment

The LGCMs analyses showed that only the Non-reactivity model had acceptable fit indices (CFI = 1, TLI = 1, RMSEA < 0.001, SRMR = 0.067), whereas FFMQ total score and the other subscale models did not fit well (see **Table 2**). For Non-reactivity, the mean initial score was 21.75. The mean slope was 0.85, which was significantly different from zero (p < 0.001), suggesting a steady increase of Non-reactivity over time in the full sample. The value 0.85 can be interpreted as an average of 0.85 increase of Non-reactivity subscale score per unit of time. The variance of the intercept was 7.78 (p = 0.002), indicating significant individual variability of initial Non-reactivity score. The variance of slope and its covariance with intercept was not significant (p = 0.12 and p = 0.701, respectively). There was no significant group difference on the initial Non-reactivity subscale score (β = −1.36, p = 0.169). However, the factor Group (0 = MBSR, 1 = waitlist) showed a significant effect on the slope for Non-reactivity (β = −0.34, p = 0.019), indicating that the MBSR group increased faster than the waitlist group on Non-reactivity subscale score. Taken together, there was individual variability in Non-reactivity at the initial level, but the groups did not differ in the initial Non-reactivity score. On average, the slope grew over time. There was no individual difference in the growth rate. Group had a significant effect on the growth rate. The MBSR group increased at a faster speed than the waitlist control on the Non-reactivity score (see **Table 3**).

TABLE 2 | Model fits based on the latent growth curve model of FFMQ scales.

Variables	χ^2	df	CFI	TLI	RMSEA	SRMR
NR	5.16	7.00	1.00	1.02	0.001	0.07
FT	35.54***	7.00	0.72	0.61	0.30	0.40
NJ	35.13***	7.00	0.74	0.63	0.30	0.23
OB	18.12**	7.00	0.91	0.87	0.19	0.12
DE	38.69***	7.00	0.68	0.54	0.32	0.18
AW	74.86***	7.00	0.45	0.21	0.47	0.49

*NR = the Non-reactivity subscale score, FT = the FFMQ total score, NJ = the Non-judgment subscale score, OB = the Observing subscale score, DE = the Describing subscale score, AW = the Acting with Awareness subscale score. **p < 0.01, ***p < 0.001.*

The Effect of MBSR on Perceived Stress and Cognitive Flexibility

For the CPSS scores, there was a significant main effect of Time ($F_{(1,52)}$ = 313.78, p < 0.001, partial η^2 = 0.86, 95% CI: 0.78–0.9), but the Group effect ($F_{(1)}$ = 0.001, p = 0.99, partial η^2 = 0.001, 95% CI: −0.55 to 0.55) and Time by Group interaction effects were not significant ($F_{(1,52)}$ = 1.17, p = 0.29, partial η^2 = 0.02, 95% CI: 0–0.15).

For the CFI scores, the Time effect ($F_{(1,52)}$ = 59.86, p < 0.001, partial η^2 = 0.53, 95% CI: 0–0.15), Group effect ($F_{(1)}$ = 7.03, p = 0.01, partial η^2 = 0.12, 95% CI: 1.25–2.57) and Time by Group interaction effect were significant ($F_{(1,52)}$ = 4.27, p = 0.04,

TABLE 1 | Demographical and descriptive data for the MBSR and waiting-list group at baseline.

Variables	MBSR (*n* = 26)	Waiting-list controls (*n* = 28)	*t*/X²	*p*	Cohen's *d*
Age	34.12 (7.63)	33.6 (8.24)	0.24	0.81	0.07
Gender (% Female)	69.23%	72.41%	−0.26	0.8	/
Educational years	17.82 (2.29)	17.93 (1.92)	−0.2	0.84	−0.05
Per capita monthly income (RMB)	21, 653.94 (30, 479.14)	17, 975.95 (19, 968.86)	0.54	0.6	0.15
FFMQ total score	107.88 (13.79)	110.95 (13.73)	−0.82	0.41	−0.22
Observing	24.65 (5.96)	25.67 (5.42)	−0.66	0.52	−0.18
Describing	23.12 (2.98)	23.25 (2.69)	−0.17	0.86	−0.05
Acting with awareness	17.73 (3.98)	18.63 (6.58)	−0.6	0.55	−0.16
Non-reactivity	20.35 (2.8)	19.62 (4.26)	0.74	0.46	0.2
Non-judgment	22.04 (5.42)	23.79 (6.13)	−1.12	0.27	−0.31
CFI	68.92 (4.46)	66.96 (5.87)	1.36	0.18	0.37
CPSS	43.96 (4.35)	44.74 (4.27)	−0.67	0.51	−0.18

Gender was presented with Percentage, the other variables were presented with Mean (SD). MBSR = The Mindfulness Based Stress Reduction; FFMQ = The Five Facet Mindfulness Questionnaire, CFI = The Cognitive Flexibility Inventory, CPSS = The Chinese Perceived Stress Scale.

TABLE 3 | Parameter estimates based on latent growth curve model of FFMQ scales.

	Estimate	SE	t	p
NR				
Mean				
Intercepts	21.75	1.60	13.59	< 0.001***
Slope	0.85	0.23	3.67	< 0.001***
Variances				
NR1	3.56	1.79	1.99	0.047*
NR2	4.24	1.21	3.52	< 0.001***
NR3	4.06	1.34	3.03	0.002**
NR4	7.64	2.40	3.19	0.001**
Intercepts	7.78	2.52	3.09	0.002**
Slope	0.09	0.06	1.56	0.12
Covariance				
Intercept with slope	−0.12	0.31	−0.38	0.701
Regression				
Intercept on group	−1.36	0.99	−1.38	0.169
Slope on group	−0.34	0.14	−2.34	0.019*
FT				
Mean				
Intercepts	117.87	5.26	22.43	< 0.001***
Slope	5.17	0.79	6.54	< 0.001***
Variances				
FT1	422.34	87.08	4.85	< 0.001***
FT2	46.84	16.23	2.89	0.004**
FT3	56.08	20.30	2.76	0.006**
FT4	277.43	56.44	4.92	< 0.001***
Intercepts	−16.67	38.65	−0.43	0.666
Slope	−2.97	1.01	−2.93	0.003**
Covariance				
Intercept with slope	26.79	5.22	5.13	< 0.001***
Regression				
Intercept on group	−0.41	3.24	−0.13	0.9
slope on group	−2.02	0.49	−4.16	< 0.001***
NJ				
Mean				
Intercepts	24.04	1.48	16.23	< 0.001***
Slope	1.55	0.45	3.45	0.001**
Variances				
NJ1	37.09	7.90	4.69	< 0.001***
NJ2	24.76	5.04	4.91	< 0.001***
NJ3	25.34	5.49	4.62	< 0.001***
NJ4	−5.78	4.98	−1.16	0.246
Intercepts	−12.12	4.32	−2.81	0.005**
Slope	0.69	0.25	2.71	0.007**
Covariance				
Intercept with slope	0.33	0.75	0.43	0.665
Regression				
Intercept on group	0.32	0.91	0.35	0.725
Slope on group	−0.70	0.28	−2.52	0.012**
OB				
Mean				
Intercepts	25.29	2.82	8.96	< 0.001***
Slope	0.84	0.29	2.95	0.003**
Variances				
OB1	16.45	4.29	3.83	< 0.001***
OB2	3.51	1.60	2.20	0.028*
OB3	7.57	2.24	3.38	0.001**
OB4	16.37	4.29	3.82	< 0.001***
Intercepts	25.43	7.21	3.53	< 0.001***
Slope	−0.03	0.09	−0.28	0.783
Covariance				
Intercept with slope	−0.14	0.61	−0.22	0.823
Regression				
Intercept on group	−0.69	1.74	−0.40	0.693
Slope on group	−0.33	0.18	−1.90	0.057
DE				
Mean				
Intercepts	22.86	1.49	15.37	< 0.001***
Slope	0.98	0.21	4.64	< 0.001***
Variances				
DE1	8.66	2.63	3.29	0.001**
DE2	13.69	3.25	4.22	< 0.001***
DE3	10.40	2.88	3.61	< 0.001***
DE4	9.49	3.02	3.14	0.002**
Intercepts	2.15	2.69	0.80	0.424
Slope	−0.07	0.07	−0.95	0.342
Covariance				
Intercept with slope	1.35	0.35	3.81	< 0.001***
Regression				
Intercept on group	0.47	0.92	0.51	0.607
Slope on group	−0.13	0.13	−1.01	0.315
AW				
Mean				
Intercepts	19.76	0.93	21.21	< 0.001***
Slope	1.24	0.36	3.45	001**
Variances				
AW1	54.16	10.44	5.19	< 0.001***
AW2	16.21	3.25	4.99	< 0.001***
AW3	2.79	2.51	1.11	0.226
AW4	32.54	6.29	5.17	< 0.001***
Intercepts	−23.22	4.92	−4.72	< 0.001***
Slope	−0.28	0.17	−1.63	0.104
Covariance				
Intercept with slope	4.21	0.83	5.10	< 0.001***
Regression				
Intercept on group	0.80	0.57	1.40	0.163
Slope on group	−0.36	0.22	−1.60	0.109

*NR = the Non-reactivity subscale score, FT = the FFMQ total score, NJ = the Non-judgment subscale score, OB = the Observing subscale score, DE = the Describing subscale score, AW = the Acting with Awareness subscale score. 1–4 = time points, *p < 0.05, **p < 0.01, ***p < 0.001.*

partial $\eta^2 = 0.08$, 95% CI: 0–0.23). Follow-up *t*-tests showed that CFI scores increased significantly from pre- to post-treatment for both groups (*ps* < 0.001). However, the MBSR group scored higher than the waitlist control group at post-treatment ($p = 0.003$) (see **Figure 2**).

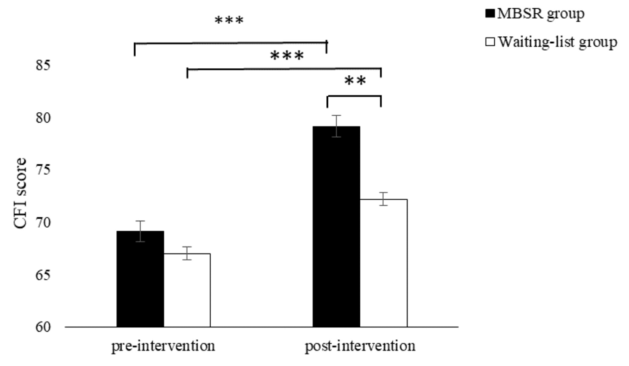

FIGURE 2 | The Cognitive Flexibility Inventory scores as a function of Time and Group. Error bars represent standard error of the mean. $^{**}p < 0.01$ and $^{***}p < 0.001$.

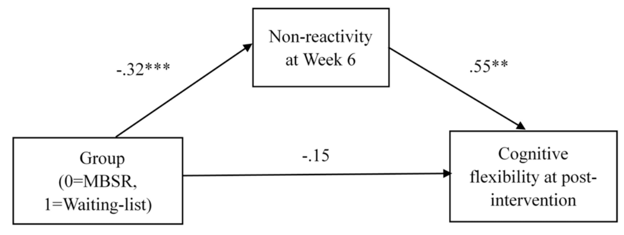

FIGURE 3 | Path analysis illustrating the mediation effect of Non-reactivity at Week 6 on the relationship of MBSR training and cognitive flexibility. $^{**}p < 0.01$ and $^{***}p < 0.001$.

The Mediating Effects of Non-reactivity and Non-judgment on the Relationship of MBSR and Cognitive Flexibility

The effect of MBSR on cognitive flexibility was not mediated by Non-reactivity at Week 3. The corresponding fit indices were reasonably good ($\chi^2_{(3)} = 16.08$, $p < 0.001$, CFI = 1, RMSEA < 0.001, SRMR < 0.001). However, the indirect effect was not significant ($ab = -0.07$, SE = 0.05, $p = 0.14$), despite a trend toward improved Non-reactivity at Week 3 via MBSR ($a = -0.24$, SE = 0.14, $p = 0.08$), and a statistically significant prediction on cognitive flexibility via Non-reactivity at Week 3 ($b = 0.28$, SE = 0.09, $p = 0.002$). The power of the indirect effect of Non-reactivity at Week 3 was 0.23.

There was a full mediation effect of Non-reactivity at Week 6. The model fit the data well ($\chi^2_{(3)} = 39$, $p < 0.001$, CFI = 1, RMSEA < 0.001, SRMR < 0.001). A significant intervention effect of MBSR on Non-reactivity at Week 6 was found ($a = -0.32$, SE = 0.11, $p = 0.003$), suggesting that MBSR improved Non-reactivity at Week 6. Furthermore, Non-reactivity at Week 6 positively predicted cognitive flexibility at post-treatment ($b = 0.55$, SE = 0.09, $p < 0.001$). The improvement of cognitive flexibility at post-treatment accounted by MBSR via Non-reactivity at Week 6 was significant ($ab = -0.18$, SE = 0.07, $p = 0.008$). Controlling for the mediating effect of Non-reactivity at Week 6, there was no significant association between group and cognitive flexibility at post-treatment ($c' = -0.15$, SE = 0.08, $p = 0.06$), indicating a full mediation effect by Non-reactivity at Week 6 (see **Figure 3**). The mediating effect of Non-reactivity at Week 6 accounted for 53.94% of the total effect between group and cognitive flexibility. The power of the indirect effect of Non-reactivity at Week 6 was 0.69.

The effect of MBSR on cognitive flexibility was not mediated by Non-judgment at Week 3. Despite the good model fit ($\chi^2_{(3)} = 24.62$, $p < 0.001$, CFI = 1, RMSEA < 0.001, SRMR < 0.001), the indirect effect of Non-judgment at Week 3 was not significant ($ab = -0.01$, SE = 0.06, $p = 0.82$). The power of the indirect effect of Non-judgment at Week 3 was 0.04. The failure to find a significant mediating effect might be due to the disassociation between group and Non-judgment at Week 3 ($a = -0.03$, SE = 0.13, $p = 0.82$), indicating that there were no differentiated effects of MBSR training or waitlist assignment on Non-judgment at Week 3. There was a significant association between Non-judgment at Week 3 and cognitive flexibility at post-treatment ($b = 0.45$, SE = 0.07, $p < 0.001$).

Similar to Week 3, there was no mediating effect of Non-judgment at Week 6 on group and cognitive flexibility at post-treatment. The model fit the data well ($\chi^2_{(3)} = 13.48$, $p < 0.001$, CFI = 1, RMSEA < 0.001, SRMR < 0.001), but the indirect effect did not reach a significant level ($ab = -0.09$, SE = 0.08, $p = 0.27$). The power of the indirect effect of Non-judgment at Week 6 was 0.17. Despite the fact that Non-judgment at Week 6 predicted cognitive flexibility at post-treatment ($b = 0.66$, SE = 0.11, $p < 0.001$), improvements in Non-judgment at Week 6 could not be differentiated from waitlist group ($a = -0.13$, SE = 0.11, $p = 0.24$). Model fit indices please see **Table 4**.

DISCUSSION

The present work examined the efficacy of MBSR on cognitive flexibility in non-clinical stressed populations and the mediating effects of Non-reactivity and Non-judgment in explaining this effect. We put forward three hypotheses. First, we hypothesized that MBSR would be effective in improving cognitive flexibility, which was supported by the data. MBSR training had an immediate effect on cognitive flexibility with a medium effect size. Results also showed that compared with waitlist controls, MBSR training did not have incremental effect on stress reduction. Our second hypothesis was that Non-reactivity during intervention mediated the relationship between intervention group and cognitive flexibility. This hypothesis was partly supported. Non-reactivity at Week 3 did not mediate the association between Group and cognitive flexibility. However, Non-reactivity at Week 6 fully mediated the relationship between group and cognitive flexibility, which explained 53.94% of overall variances. Third, we hypothesized that Non-judgment during intervention mediated the relationship between group and cognitive flexibility, which was not supported by the data. Neither Non-judgment at Week 3 nor that at Week 6 mediated the association between MBSR training and cognitive flexibility.

TABLE 4 | Model fit indices and standardized path coefficients for hypothesized mediation models.

Model	χ^2/df	CFI[2]	RMSEA	SRMR	Standardized path coefficients	IND %
IV: Group	5.36	1	< 0.001	< 0.001	*a* = −0.24, SE = 0.14, *p* = 0.08	20.3
Mediator: Week 3 Non-reactivity					*b* = 0.28, SE = 0.09, *p* = 0.002**	
Outcome: Post-test CFI[1]					*c′* = −0.26, SE = 0.09, *p* = 0.004**	
					ab = −0.07, SE = 0.05, *p* = 0.14	
IV: Group	13	1	< 0.001	< 0.001	*a* = −0.32, SE = 0.11, *p* = 0.003**	53.94
Mediator: Week 6 Non-reactivity					*b* = 0.55, SE = 0.09, *p* < 0.001**	
Outcome: Post-test CFI[1]					*c′* = −0.15, SE = 0.08, *p* = 0.06	
					ab = −0.18, SE = 0.07, *p* = 0.008**	
IV: Group	8.2	1	< 0.001	< 0.001	*a* = −0.03, SE = 0.13, *p* = 0.82	4.24
Mediator: Week 3 Non-judgment					*b* = 0.45, SE = 0.07, *p* < 0.001**	
Outcome: Post-test CFI[1]					*c′* = −0.32, SE = 0.08, *p* < 0.001***	
					ab = −0.01, SE = 0.06, *p* = 0.82	
IV: Group	4.49	1	< 0.001	< 0.001	*a* = −0.13, SE = 0.11, *p* = 0.24	26.97
Mediator: Week 6 Non-judgment					*b* = 0.66, SE = 0.11, *p* < 0.001***	
Outcome: Post-test CFI[1]					*c′* = −0.24, SE = 0.09, *p* = 0.005**	
					ab = −0.09, SE = 0.08, *p* = 0.27	

*IV = Independent variable, CFI[1] = The Cognitive Flexibility Inventory, CFI[2] = The Comparative fit index, RMSE a = Root-mean-square error of approximation, SRMR = Standardized root mean square residual, a = The path coefficient from IV to mediator, b = The path coefficient from mediator to outcome, c′ = The path of IV to outcome controlling for mediator, ab = a*b (the indirect effect), IND% = The percentage of the indirect effect on the total effect. **p < 0.01, ***p < 0.001.*

Using a randomized controlled trial, we provided evidence that the MBSR program is effective in cultivating ability to generate alternative explanations. First, MBSR training lead to a significantly greater improvement in cognitive flexibility than waitlist controls. Second, the MBSR group achieved approximately 10 points increase in CFI from pre- to post-treatment, with a medium effect size. Our finding is consistent with another study that reported an 11-point increase in CFI for MBCT training group (Shapero et al., 2018). This finding is consistent with the general idea that MBI should improve the tendency to be mindful in everyday life, which might result in improvements in psychological outcomes, including responding adaptively to life events. Taken together, MBSR appears to be particularly effective in cultivating ability to perceive stressful life events as controllable and to form alternative explanations for stressful situations.

Unexpectedly, we did not replicate MBSR's well-documented effect on psychological distress reduction (Chiesa and Serretti, 2009; Khoury et al., 2015; Ma et al., 2018), which is surprising. Four explanations are possible. First, demographical characteristics and baseline mindfulness might have confounded the treatment effect on the results. We conducted follow-up repeated-measure ANOVAs to include each of the potential covariates (e.g., age, gender, education, family income, initial level of FFMQ). The results showed that the Time by Group interaction was not significant (*p*s = 0.14–0.21), indicating that demographics and initial mindfulness level did not confound the training effect on stress. Second, participants in the MBSR group might have had a low basic stress level, which might lead to limited health benefits from the mindfulness training (Yu et al., 2019). We compared the baseline stress level with previous studies in stressed population without psychiatric disorders (Marcus et al., 2003; Chang et al., 2004; Yu et al., 2019). The abovementioned studies reported that the MBSR group had an average item score ranging from 1.8 to 2.7 points approximately at pre-treatment, whereas our sample in the MBSR group had an average item score of about 3 points, indicating a relative higher stress level, which did not support this explanation. Third, it is possible that participants in the waitlist group also experienced stress reduction over time. In fact, the waitlist controls in our study experienced substantially reduced stress from pre- to post-treatment (average item scores, pre-treatment: 3.2 points, post-treatment: 2.2 points). However, Yu et al. (2019) reported that waitlist controls perceived slightly higher stress from pre- to post-treatment (average item scores, pre-treatment: 1.8 points, post-treatment: 1.9 points). It is possible that the stress reduction effect for the waitlist controls in our study was driven by natural decay of stress or self-regulation, which warrants further investigations. Fourth, our assessment of stress (CPSS) emphasized the cognitive appraisal (e.g., uncontrollable, unpredictable, and unresolvable) of difficult situations, which did not include other aspects of stress responses (e.g., somatization). Therefore, it is possible that our assessment method was not sensitive enough to capture the severity of stress. These speculations warrant further investigations.

Non-reactivity at Week 6 during intervention had a full mediation effect on intervention group and cognitive flexibility. Our finding suggests that through 6 weeks of mindfulness practice, the Non-reactivity skill, which is about allowing experiences to come and go by themselves, without being attached to or changing them, was a successful and critical means to foster cognitive flexibility. These findings are in accordance with neuroimaging studies. For example, Creswell et al. (2007) found that individuals who showed less openness and acceptance to experiences, exhibited stronger activation in limbic systems when labeling negative thoughts and experiences. Whereas individuals who processed high openness and acceptance to experience exhibited stronger activation in prefrontal regions and inhibition of the limbic responses, suggesting successful inhibiting of habitual responses.

It is important to note that Non-reactivity at Week 3 did not mediate the relationship between intervention group and cognitive flexibility. This finding is not surprising. From path analysis statistics, failure to detect a mediation effect might be due to a disassociation between group and Non-reactivity at Week 3, which indicates the change of Non-reactivity was not attributed to the lack of effectiveness of MBSR. Tracing back to the 8-week MBSR program (Kabat-Zinn, 1990), the first three weeks introduced a small part of Non-reactivity skills. For example, participants were guided to experience bodily sensations, including exploring pain feelings and letting go of the reaction of changing the feeling of pain. In addition, participants were gradually guided to explore and experience emotional experiences, and to not take immediate action. But the most important exercises of Non-reactivity skills were introduced starting in Week 5. For instance, participants were guided to face the life stress, accept their own stress response, and temporarily not react so that they can get rid of the habitual reactions and eventually create a new way of coping. Therefore, for the MBSR group, the improvement of Non-reactivity from pre-treatment to Week 3 was far more subtle (mean at pre-treatment: 20.35, mean at Week 3: 21.56) than Week 6.

Our findings are consistent with the notions that Non-reactivity, cultivated by mindfulness, would alter the association between the perception and appraisal for the environmental stimuli (Lutz et al., 2015). Furthermore, this finding is convergent with growing evidence that non-reaction to emotion leads to beneficial psychological outcomes. For example, after a 3-month training, only Non-reactivity in FFMQ predicted greater reduction in mood symptoms in a present awareness mindfulness training group as compared to a progressive muscle relaxation training group (Gao et al., 2018). It has been suggested that adopting accepting-emotion strategies reduced negative affect (Campbell-Sills et al., 2006), and alleviated anxiousness and avoidance reactions (Levitt et al., 2004). In addition, prior research indicated that the improvement of the Non-reactivity facet from pre- to post-treatment mediated the effect of mindfulness training on decreasing depression symptoms from pre- to post-treatment in clinical samples (Heeren et al., 2015). These findings suggest that Non-reactivity may be a powerful mechanism of mindfulness. The underlying process might be that higher levels of Non-reactivity make it easier for people to disengage from established but unhelpful responses (Malinowski, 2013; Makowski et al., 2019), switch mental states adaptively, inhibit habitual responses, and thus have time to improve the ability to generate new appraisals and solutions to difficult situations. It is possible that the treatment targeted aspects directly linked to the content of the items included in the CFI. The CFI had a moderately positive correlation with the FFMQ at baseline ($r = 0.35$, $p = 0.008$), indicating a link between them. These speculations warrant further investigation. In summary, Non-reactivity is one important component of the effectiveness of MBSR training on cognitive flexibility.

For the longitudinal trajectories of FFMQ scales across four time points, we found the only the Non-reactivity scale fitted the latent curve model well. There was substantial individual variability in the initial score. All individuals increased on Non-reactivity at the same rate. However, the inclusion of group as a covariate resulted in a statistically significant growth rate. Specifically, the MBSR group increased at a faster speed than the waitlist controls.

Contrary to our hypothesis, Non-judgment during intervention did not mediate the effect of intervention group and cognitive flexibility. We make two speculations in explaining this finding. First, because some participants missed some assessment points, results might be biased. This is especially true for the waitlist control group, because those participants who persisted might have had greater interests in mindfulness than those who discontinued. Therefore, they might have been motivated to learn more about mindfulness from reading books or other materials, in which Non-judgment might be mentioned frequently. Over time, they would report a higher level Non-judgment skills, making the MBSR training effect of Non-judgment less notable. Second, improvements of Non-judgment at Week 3 and Week 6 were not explained by the efficacy of MBSR training. This speculation is supported by the fact that "a" path coefficients were not significant (for Non-judgment at Week 3: $a = -0.03$, SE = 0.13, $p = 0.82$; for Non-judgment at Week 6: $a = -0.13$, SE = 0.11, $p = 0.24$).

Several limitations should be considered. The present study had a small sample size, which might lower the statistical power. Our sample comprised of mostly women and highly educated participants, therefore conclusions should be taken with caution if generalizing to heterogeneous samples. We recruited participants without DSM-diagnosed mental illness, which may weaken the motivation of engagement with MBSR. In terms of practice duration, previous literatures showed that college students practiced 1.5 times/week (13 min/time) on average (Solhaug et al., 2019), whereas the mean practice durations in smokers were 20.89 min/day (Goldberg et al., 2014). Unfortunately, we did not collect the data of practice duration in this study to examine this issue. We used waitlist group (without any treatment) as controls, which could not explore the specific effect of mindfulness training. Measures were self-report instruments, which might be biased by retrospective memory and we did not assess actual life events. Future studies should consider measuring stressful life events, because cognitive flexibility may not only be trait-like stable but also context dependent (Schultz and Searleman, 2002). Furthermore, the missing outcome data might have biased the estimation of the treatment effect. Follow-up data were not collected, thus the maintenance effect remains in question. Future studies should use larger samples to test the replicability of this finding. Samples should include larger proportions of men and low-educated populations to test the generalization of the conclusion. Active controls such as psycho-education or relaxation training should be taken into account to test the specific effect of MBSR. Follow-up assessments would be needed to explore the maintenance effect, or the long-term benefits of improving cognitive flexibility. Finally, future studies are needed to examine other facets of mindfulness and their specific effects on stress and emotions (Carpenter et al., 2019).

Despite the abovementioned limitations, our findings exhibit sufficient statistical power and indicated that MBSR training is effective in improving flexible cognitions (perceived control and alternative explanations and solutions) confronting stressful life events, with a medium effect size. Furthermore, our findings suggest that Non-reactivity is the primary focus for MBSR training to increase cognitive flexibility. Our findings bridge knowledge gaps in prior studies by elucidating that Non-reactivity mediated the efficacy of mindfulness training on cognitive flexibility.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This research involves human participants. All procedures performed in studies involving human participants were in accordance with the ethical standards of the research committee (the Association for Ethics and Human and Animal Protection in School of Psychological and Cognitive Sciences, Peking University, 2018-10-02) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

AUTHOR CONTRIBUTIONS

YZ collected, analyzed, and interpreted the data, and wrote the drafts of the manuscript. PL collected the data. SH collaborated in the commenting on and editing the drafts of the manuscript. XL designed the study, taught part of the MBSR program, interpreted the findings, and commented critically on the drafts 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/fpsyg.2020.01053/full#supplementary-material

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Cognition and Brain Activation in Response to Various Doses of Caffeine: A Near-Infrared Spectroscopy Study

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Caffeine, which is widely used for enhancing athletic performance, has been suggested to have a positive impact on cognition via stimulating the brain. However, no study published to date has explored the effects of different doses of caffeine ingestion on brain activation via cortical hemodynamics. The purpose of the present crossover, double-blind study was to investigate the effects of low, moderate, and high doses of caffeine ingestion on cognitive performance and brain activation. Ten healthy male subjects ingested placebo or caffeine (3, 6, or 9 mg/kg body mass). The effects of each treatment condition were evaluated by Stroop tasks before and 60 min after the ingestion of caffeine. Reaction time (RT) and accuracy of responses to congruent and incongruent stimuli were assessed. As an index of brain activation with cognition, levels of oxygenated hemoglobin (HbO) were measured via near-infrared spectroscopy. A 4 × 2 mixed ANOVA revealed that there were significant interaction effects for RT in both incongruent and congruent conditions ($P < 0.01$, $P\eta^2 = 0.384$; $P < 0.05$, $P\eta^2 = 0.259$; and $P < 0.05$, $P\eta^2 = 0.309$). Both 3 and 6 mg/kg of caffeine ingestion significantly decreased RT to incongruent stimuli. The only dose of caffeine to decrease RT in response to congruent stimuli was 3 mg/kg. None of the doses of caffeine administered affected accuracy of responses to incongruent or congruent stimuli. Under the congruent stimulus condition, ingestion of 3 mg/kg of caffeine significantly increased mean HbO in the dorsolateral prefrontal cortex, frontal pole area, ventrolateral prefrontal cortex ($P < 0.01$, $P\eta^2 = 0.319$; $P < 0.05$, $P\eta^2 = 0.263$; and $P < 0.05$, $P\eta^2 = 0.259$, respectively). None of the doses of caffeine investigated affected HbO under the incongruent stimulus condition. Ingestion of low-dose caffeine has greater effects on cognition and brain activation than moderate and high doses of caffeine, suggesting that low-dose caffeine may be a selective supplement in enhancing executive function and prefrontal activities.

Keywords: caffeine, different doses, cognition, brain activation, near-infrared spectroscopy

INTRODUCTION

Caffeine is widely used by athletes for improving exercise performance. Administration of 3–13 mg/kg body mass caffeine increases exercise performance during intensive running or cycling by 20–50% (Sökmen et al., 2008). Graham and Spriet (1995) investigated the effects of low, moderate, and high doses of caffeine on prolonged exercise capacity. They found that ingestion of 3 or 6 mg/kg of caffeine improved time to exhaustion, whereas 9 mg/kg of caffeine did not. There results indicated that the effect of low-dose caffeine ingestion had the similar ergogenic effect as moderate dose, which could improve physical ability. Excellence in sport performance requires not only physical and motor capabilities but also sensory–cognitive skills (Moscatelli et al., 2016). However, to our knowledge, no study examined the effects of low, moderate, and high doses of caffeine on cognition until now.

Stimulation of the central nervous system (CNS) has been proposed to explain caffeine's ergogenic effects (Kalmar and Cafarelli, 2004). Caffeine acts as a central stimulant and enhances cognitive and psychomotor functioning, particularly during mental and physical fatigue, through effects that enhance alertness and vigilance. These findings suggest that the exercise performance-enhancing effects of caffeine stem from the compound's ability to alter CNS function (Hogervorst et al., 2008).

The action of caffeine on the brain suggests an effect on cognitive performance. Cognition includes executive functioning (EF), decision making, and creativity. Executive functioning is important during exercise and can be affected by prolonged exercise (Yanagisawa et al., 2010). Reports in the scientific literature present inconsistent findings in relation to the effects of caffeine ingestion on the Stroop task performance, a measure of executive function. Some studies involving cognitive inhibition or interference conditions report faster or potential fast reaction times (RTs) with the use of caffeine (Hasenfratz and Bättig, 1992; Kenemans et al., 1999; Hogervorst et al., 2008; Dixit et al., 2012; Dodd et al., 2015; Souissi et al., 2019), whereas others report no change at all (Edwards et al., 1996; Bottoms et al., 2013). Differences in outcomes between studies may be related to the sensitivity of the cognitive tests used or the dose of caffeine administered, and more studies need to examine effects of caffeine on cognition.

The effects of caffeine on cognition may be related to the enhancement of brain activation. Early studies postulated that the effects of caffeine on brain activation depend on the complex interaction of neuronal and vascular responses. These responses may vary among brain regions, introducing an additional layer of complexity (Laurienti et al., 2003; Koppestaetter et al., 2010). Caffeine acts as a non-adenosine receptor antagonist. It blocks adenosine receptors and excites neuro-stimulants (Dunwiddie and Masino, 2001). Moreover, caffeine acts as a vasoconstrictor via blocking adenosine 2A and 2B receptors, resulting in decreased cerebral blood flow (CBF) (Laurienti et al., 2002; Pelligrion et al., 2010). The interaction of caffeine with neural and vascular systems has direct effects on neural connectivity during resting states as well as cognitive activation (Haller et al., 2014).

Brain activation is measured using neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and near-infrared spectroscopy (NIRS). Using blood oxygen level-dependent (BOLD) fMRI, Diukova et al. (2012) found that caffeine ingestion increased activity in the frontal cortex. The BOLD signal is a complex functional measurement of changes in neural activity, oxygen metabolism, cerebral blood volume, and CBF (Buxton et al., 2004). The balance between blood levels of oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR) is a critical determinant of the BOLD response. Levels of HbO and HbR may be measured with NIRS to investigate components underlying the BOLD response. NIRS studies that evaluated the responses of participants on various tests of cognition have reported conflicting results for the effects of caffeine on HbO and HbR (Niioka and Sasaki, 2003; Higashi et al., 2004; Heilbronner et al., 2015).

To our knowledge, no NIRS-based study published to date has explored the effects of low, moderate, and high doses of caffeine on brain activation during cognitive tasks. The purpose of the present study was to investigate the effects of various doses of caffeine ingestion on brain activation and cognitive performance. We hypothesized that low-dose caffeine ingestion had similar effects as moderate dose, which could improve executive functioning and brain activation.

MATERIALS AND METHODS

Subjects

Ten healthy, non-smoking male subjects (age 20 ± 1 year, height 1.73 ± 0.20 m, and weight 70.5 ± 4.8 kg) participated in this study. They were non-users (ingesting < 50 mg of caffeine/day). The sample size used was calculated by G-Power software [effect size (ES) = 0.15, power = 0.80; Faul et al., 2007]. Subjects were required to visit the laboratory with an empty belly and to abstain from drinking beverages containing caffeine and from use of other psychoactive substances or medication for at least 24 h before every experimental trial. All subjects were fully informed of the nature and possible risks of the study. After that, written informed consent was obtained from all subjects before study enrollment. The study followed the ethical guidelines of the Declaration of Helsinki and was approved by the local ethics committee at Shanghai University in Sport, Shanghai, China (No. 2016008).

Protocol

Subjects visited the laboratory four times, at the same time of day. When participants arrived in the dimly lit room where experiments were to be conducted, they were seated in a comfortable chair in front of a computer monitor. After the NIRS optode grid had been positioned on the subjects' head, they performed the Stroop familiarization trial. In order to obtain baseline measurements of performance on the Stroop task, each subject sat quietly for 5 min and watched a black screen. At that point, the NIRS recording was paused, and participants ingested capsules containing placebo (calcium carbonate; CON) or 3 mg/kg (CAF3), 6 mg/kg (CAF6), or 9 mg/kg (CAF9) of caffeine with 200 ml of water (PRE). After a 60-min delay, during which the optode grid remained in place, participants once again performed the same Stroop task (POST). The crossover, double-blind design was used in the present study. All subjects completed all experiment conditions, which were separated by 1 week to ensure drug washout period.

Drugs

Caffeine hydrate (Wako Pure Chemical Industries, Ltd., Osaka, Japan) and calcium carbonate, which are white powder, were used in this study. The dosage of each condition was calculated according to the weight. In the CON condition, 9 mg/kg of calcium carbonate was put into three red capsules. In the CAF3 condition, both 3 mg/kg of caffeine and 6 mg/kg of calcium carbonate were put into three red capsules. In the CAF6 condition, both 6 mg/kg of caffeine and 3 mg/kg of calcium carbonate were put into three red capsules. In the CAF9 condition, 9 mg/kg of caffeine was put into three red capsules. In this way, researchers and subjects could not identify caffeine according to the appearance and taste of the capsule.

Stroop Task

The Stroop task is widely used to evaluate selective attention, cognitive flexibility, and processing speed (Pauw et al., 2015). It was programmed and performed on E-prime 1.0 software (Psychology Software Tools, Pittsburgh, PA, United States). Each trial was displayed as follows: a fixed cross in the center of the screen for 500 ms and a stimulus duration for 500 ms. There were two kinds of stimuli in current study: congruent and incongruent conditions. The congruent condition is composed of three Chinese color words (i.e., 绿 for green, 蓝 for blue, and 红 for red), whose color was the same to the meaning of the color words (e.g., "green" word was presented in green). And the incongruent condition consisted of the same three-color words, whose color was completely different from the meaning of the color words (e.g., "green" words were presented in blue or red). Subjects were required to figure out the presenting color of each word by using the numeric keypad as the response apparatus. And the numeric keypad featured digits "1," "2," and "3" from left to right, which correspond to the responses of "blue," "green," and "red," respectively. The subjects used the index, middle, and ring fingers of their right hand for the response of digits "1," "2," and "3." According to the previous Stroop task, the RTs on figuring out the color in the incongruent condition were longer than those in the congruent condition, as the processing of word meaning in the incongruent condition interferes with the color recognition (e.g., when "green" words were presented in red, the meaning of the green word impedes the recognition of red; Stroop, 1935; Pauw et al., 2015).

Participants performed two blocks of 120 trials. Each block included 60 congruent and 60 incongruent trials, which were randomly presented. To prevent participants from anticipating a stimulus, the interval between appearance of the fixed cross and presentation of the stimulus was randomly differed between 300 and 800 ms, with the fixed inter-stimulus interval (ISI) duration of 1,500 ms. Both RT and accuracy (ACC) were recorded for further analysis.

Hemodynamic Data Acquisition

We used a multichannel, continuous wave, NIRS instrument (NIRScout, NIRx Medical Technologies LLC, Minneapolis, MN, United States) for monitoring hemodynamic activity during performance of the task and during the resting state. The sampling rate was 3.91 Hz. The NIRS probe included 16 dual-wavelength sources (780 and 830 nm) and 15 optical detectors, which covered the frontal and parietal areas bilaterally (**Figure 1**). One emitter and one detector (3 cm apart) formed a channel. Forty channels were assessed: 20 distributed throughout the frontal area and 20 distributed throughout parietal areas. The correspondence between NIRS channel locations and specific brain regions was established by Okamoto et al. (2004, 2009) and Tsuzuki et al. (2007). Probes were set according to a 10/20 electroencephalogram system, with some adjustments to ensure that each emitter was 3 cm away from its corresponding detector (Chen et al., 2018).

Hemodynamic Data Analysis

Optical data were transformed into hemoglobin signals with arbitrary units in accordance with the modified Beer–Lambert law (Cope et al., 1988). It has been reported that HbO signals have a better signal-to-noise ratio than HbR signals (Niu et al., 2013; Schaeffer et al., 2014), so we used only HbO measurements to analysis. The HbO data were analyzed with nirsLAB software. After discontinuous shifts were removed from the time series dataset, HbO signals were bandpass-filtered between 0.01 and 0.2 Hz to remove baseline drift and physiological noise (e.g., heartbeats). Bandpass filtering was performed by a high-pass filter with a cutoff frequency of 0.01 Hz to remove low-frequency noise, such as head movement, and by a low-pass filter with a cutoff frequency of 0.2 Hz to attenuate high-frequency noise and cardiovascular artifacts (Huppert et al., 2009; Yunjie et al., 2012). Then, each subject's HbO during a given session was calculated. Hemodynamic data were then baseline-corrected based on the mean value of all signals from each block (5 s before to 15 s after the block). The HbO data were then averaged across subjects (Chen et al., 2018).

The region of interest (ROI) channels were defined as those channels with maximal HbO. After HbO was averaged across subjects, mean HbO during the congruent and incongruent conditions was subtracted from mean HbO during the resting state. The mean difference between the single-cognitive task and resting state sessions was arranged according to descending magnitude, for each channel (Chen et al., 2018). We defined channels of interest as the top 30% of channels (greatest values). The multichannel NIRS space was transformed into traditional Montreal Neurological Institute space (Cutini et al., 2011). Channels of interest were related to three ROIs on the basis of their spatial distribution relative to the automated anatomical labeling template (**Table 1**). HbO values were then averaged through channels within a given ROI.

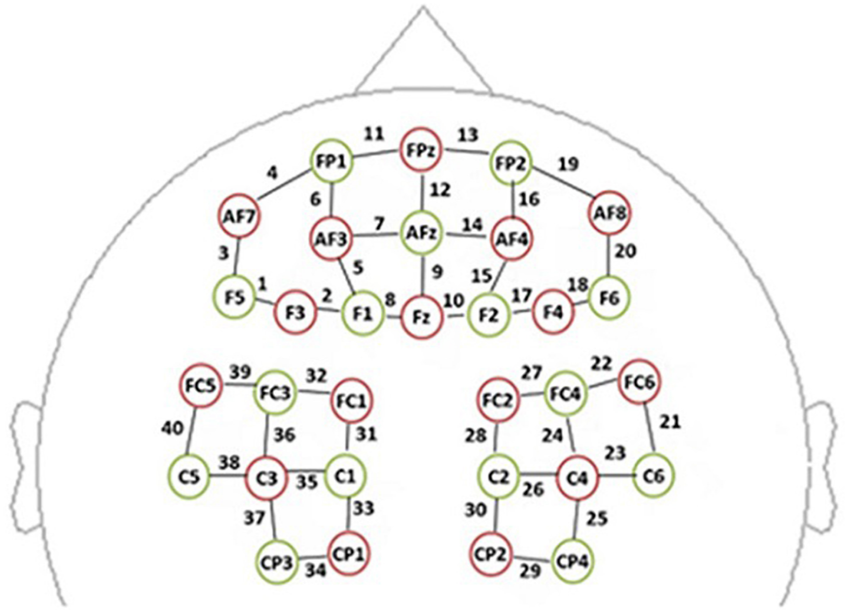

FIGURE 1 | The spatial profile of functional near-infrared spectral imaging (fNIRS) probes. The red circles indicate the 16 optical sources, the green circles indicate the 15 detectors, and the black numbers (1–40) indicate fNIRS channels. The optical sources and detectors were positioned on the international 10–20 standard positions.

Data Analysis

Statistical analyses were conducted with SPSS 20.0 software (SPSS Inc., Chicago, IL, United States). One-sample Kolmogorov–Smirnov test was used to test whether data were normally distributed. When data are not normally distributed, statistical analysis was performed on the logarithmic transformation of the data. RT, ACC and mean HbO data for all frequencies in a given ROI were subjected to repeated-measures three-way ANOVA with dose (CON/CAF3/CAF6/CAF9), time (PRE/POST), and condition (incongruent/congruent) as within subject factors to examine whether the general tendencies for the Stroop task could be reproduced in all conditions. Then alterations in RT, ACC, and averaged HbO data for all frequencies in a given ROI were subjected to 4 × 2 repeated-measures ANOVAs. For cases in which the assumption of sphericity was violated, the Greenhouse–Geisser correction was used to reduce the likelihood of a Type I error. If significant main or interaction effects were found, *post-hoc* analyses were carried out with a Bonferroni correction. Partial eta^2 ($P\eta^2$) was used as a measure of ES in the case of ANOVA. The criteria to interpret the magnitude of ES were as follows: small ($P\eta^2 = 0.01$), medium ($P\eta^2 = 0.06$), or large ($P\eta2 = 0.14$; Cohen, 1992). Data are presented as mean ± SD. Statistical significance was accepted at $P < 0.05$.

TABLE 1 | Stroop task-related regions of interest (ROIs).

ROI	Channels	Hemisphere	Location
1	5,7,14,15	Bilateral	DLPFC
2	6,11,13,14	Bilateral	FPA
3	3,4,19,20	Bilateral	VLPFC

DLPFC, dorsolateral prefrontal cortex; FPA, frontal pole area; VLPFC, ventrolateral prefrontal cortex.

RESULTS

Stroop Task Performance

The three-way ANOVA for RT and ACC demonstrated no significant interaction effects ($P = 0.201$, $P\eta^2 = 0.155$; and $P = 0.201$, $P\eta^2 = 0.155$, respectively). The ANOVA revealed that there were significant main effects of condition for RT ($P < 0.001$, $P\eta^2 = 0.882$) and ACC ($P < 0.01$, $P\eta^2 = 0.567$). These results confirmed that Stroop interference could be generally observed between the congruent and incongruent conditions.

Incongruent Condition

A 4 × 2 mixed ANOVA revealed that there was a significant interaction for RT [$F(3, 27) = 5.61$, $P < 0.01$, $P\eta^2 = 0.384$, **Table 2**]. RT of 60 min after the administration was significantly decreased after treatment with 3 mg/kg (PRE, 685.43 ± 85.95 ms; POST, 649.70 ± 96.53 ms, $P < 0.05$) or 6 mg/kg (PRE, 658.83 ± 71.93 ms; POST, 624.10 ± 84.57 ms, $P < 0.05$). There was no significant difference in RT between CAF3 and CAF6. Treatment with 9 mg/kg of caffeine did not affect RT. There was no significant interaction for ACC (**Table 2**).

Congruent Condition

We found a significant interaction for RT [$F(3, 27) = 3.14$, $P < 0.05$, $P\eta^2 = 0.259$, **Table 2**]. RT had decreased significantly at 60 min after the administration of 3 mg/kg of caffeine (PRE,

TABLE 2 | The reaction time and accuracy rate of the Stroop test.

Measurements	Condition	Dose (mg/kg)	PRE	95%CI	POST	95%CI
	Incongruent (ms)	0	643.18 ± 82.80	583.95–702.42	669.18 ± 72.47	617.34–721.02
		3	685.43 ± 85.95	623.94–746.91	649.70 ± 96.53[#]	580.65–718.75
		6	658.83 ± 71.93	607.37–710.28	624.10 ± 84.56[#]	563.61–684.59
Reaction time		9	654.54 ± 93.05	587.98–721.11	649.65 ± 104.41	574.95–724.33
	Congruent (ms)	0	582.54 ± 82.05	523.84–641.23	608.85 ± 79.50	551.98–665.72
		3	580.66 ± 79.39	523.86–637.44	553.60 ± 78.32[#]	497.57–609.63
		6	576.28 ± 67.48	528.01–624.55	580.37 ± 66.12	533.07–627.66
		9	585.74 ± 67.94	537.14–634.34	574.05 ± 78.29	518.03–630.05
	Incongruent	0	0.92 ± 0.07	0.87–0.96	0.95 ± 0.07	0.91–1.00
		3	0.94 ± 0.06	0.90–0.98	0.94 ± 0.04	0.91–0.97
		6	0.95 ± 0.04	0.92–0.97	0.93 ± 0.06	0.89–0.98
Accuracy rate		9	0.92 ± 0.05	0.89–0.96	0.95 ± 0.06	0.91–0.99
	Congruent	0	0.96 ± 0.03	0.93–0.98	0.96 ± 0.05	0.92–1.00
		3	0.97 ± 0.04	0.94–0.99	0.99 ± 0.01	0.98–1.00
		6	0.98 ± 0.04	0.95–1.00	0.98 ± 0.02	0.97–1.00
		9	0.96 ± 0.03	0.94–0.98	0.97 ± 0.03	0.95–0.99

PRE, before administration; POST, after administration. [#]Significant PRE vs. POST ($p < 0.05$). Values are mean ± SD.

580.66 ± 79.39 ms; POST, 553.60 ± 78.32 ms, $P < 0.01$). However, the administration of caffeine at doses of 6 or 9 mg/kg did not affect RT. We found no significant interaction for ACC (**Table 2**).

Near-Infrared Spectroscopy

The three-way ANOVA for ROI-1 [dorsolateral prefrontal cortex (DLPFC)], ROI-2 [frontal pole area (FPA)], and ROI-3 [ventrolateral prefrontal cortex (VLPFC)] demonstrated no significant interaction effects ($P = 0.09$, $P\eta^2 = 0.230$; $P = 0.224$, $P\eta^2 = 0.154$; and $P = 0.633$, $P\eta^2 = 0.061$, respectively). The ANOVA revealed that there was a significant main effect of condition for ROI-1 ($P < 0.05$, $P\eta^2 = 0.394$).

Incongruent Condition

A 4 × 2 mixed ANOVA revealed that there was no significant interaction for mean HbO in ROI-1 (**Figure 2A**), ROI-2 (**Figure 2B**), or ROI-3 (**Figure 2C**).

Congruent Condition

We found a significant interaction for mean HbO in ROI-1 [$F(3, 27) = 4.21$, $P < 0.01$, $P\eta^2 = 0.319$, **Figure 3A**]. In the CON group, mean HbO had significantly decreased at 60 min after administration of the placebo, as compared with baseline values. At 60 min after the administration of 3 mg/kg of caffeine, mean HbO had significantly increased. The administration of caffeine at doses of 6 or 9 mg/kg did not affect mean HbO.

A 4 × 2 mixed ANOVA revealed that there was a significant interaction for the mean HbO in ROI-2 [$F(3, 27) = 3.21$, $P < 0.05$, $P\eta^2 = 0.263$, **Figure 3B**]. Compared with baseline values, mean HbO after 60 min showed a significant decrease in the CON group. At 60 min after the administration of 3 mg/kg of caffeine, mean HbO had significantly increased. Treatment with caffeine at doses of 6 or 9 mg/kg did not affect mean HbO.

Two-factor ANOVA of mean HbO showed significant effects of dose × time [$F(3, 27) = 4.02$, $P < 0.05$, $P\eta^2 = 0.309$, **Figure 3C**]. Compared with baseline values, mean HbO had significantly decreased at 60 min in the CON group. At 60 min after treatment with 3 mg/kg of caffeine, mean HbO had significantly increased. Treatment with caffeine at doses of 6 or 9 mg/kg did not affect mean HbO.

DISCUSSION

This novel study investigated the effects of ingestion of low, moderate, or high doses of caffeine typically used by athletes on cognition and brain activation using NIRS. We found that ingestion of low doses of caffeine, but not moderate or high doses caffeine, decreased RT on the Stroop task, under the congruent and incongruent conditions, and increased mean HbO in three ROIs under the congruent condition. Ingestion of moderate doses caffeine only decreased RT on the Stroop task, under the incongruent conditions.

Low doses (≤3 mg/kg) of caffeine have been reported to improve cognition during and after strenuous exercise (Hogervorst et al., 1999, 2008). Ingestion of 3 mg/kg of caffeine, but not 6 or 9 mg/kg, decreased RT under the congruent condition on the Stroop task. This result suggests that low-dose caffeine may represent "a direct and specific 'perceptual-motor' speed or efficiency factor" (Nehlig, 2010). After consumption of low doses of caffeine, participants in our study showed decreased RT, accompanied by a significant decrease in interference effects. These findings are similar to those reported by Kenemans et al. (1999).

In this study, the ingestion of 6 mg/kg of caffeine decreased RT on the Stroop task under the incongruent condition. Nonetheless, the beneficial effects of 6 mg/kg of caffeine on cognitive performance are in dispute. Similar to the present study, Souissi et al. (2019) found that 6 mg/kg of caffeine ingestion improved RT and attention. Moreover, Ali et al. (2015) showed that 6 mg/kg of caffeine induced a tendency toward improvement in performance on the Stroop task among female athletes engaged in team

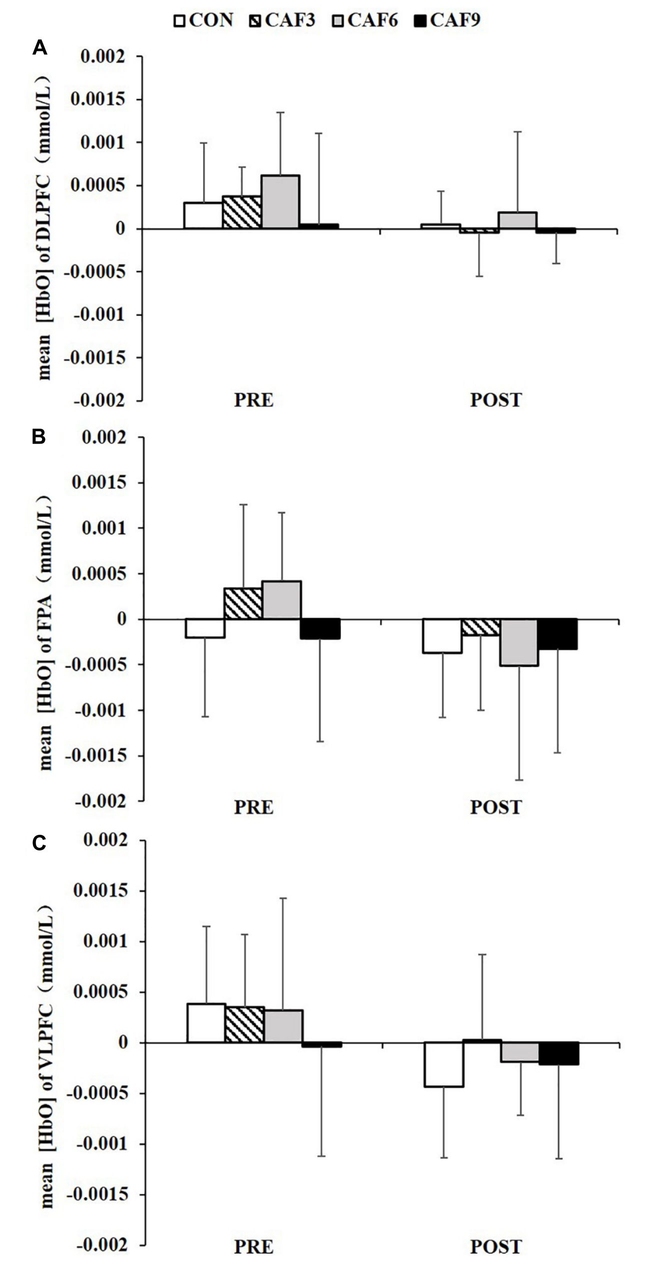

FIGURE 2 | Changes in the mean [HbO] of incongruent condition in the DLPFC **(A)**, FPA **(B)**, and VLPFC **(C)**. HbO, oxygenated hemoglobin; DLPFC, dorsolateral prefrontal cortex; FPA, frontal pole area; VLPFC, ventrolateral prefrontal cortex; PRE, before administration; POST, after administration. Values are mean ± SD.

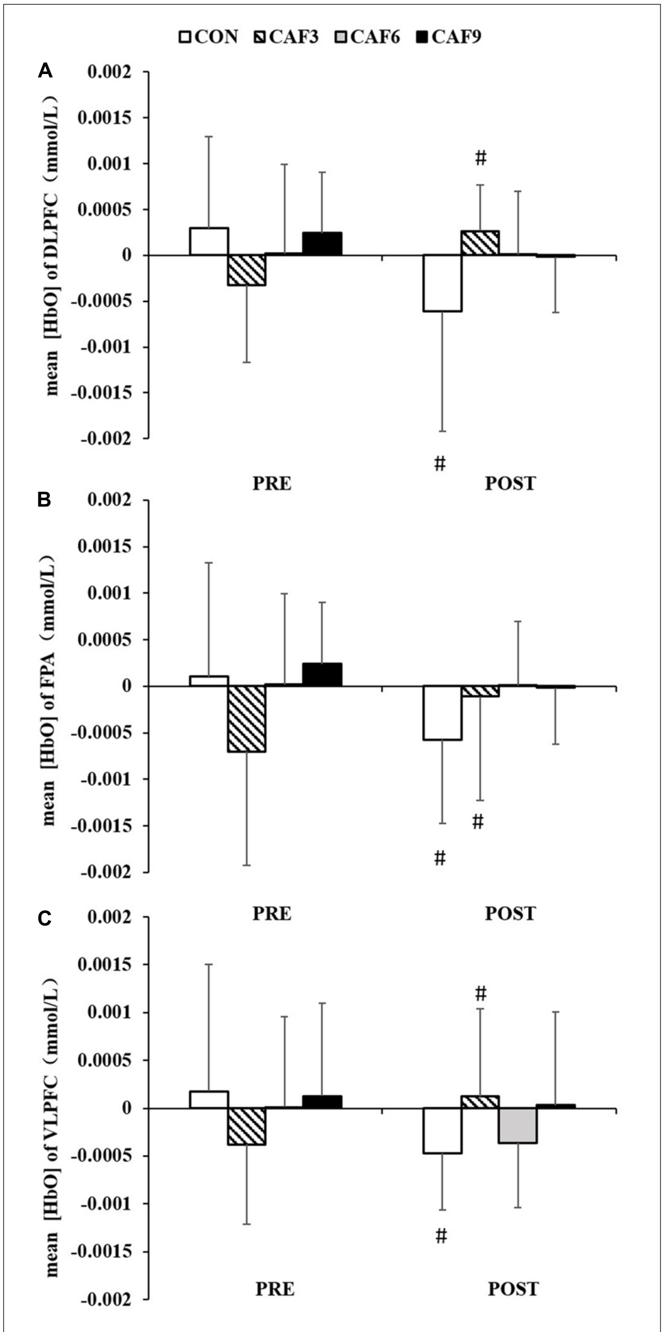

FIGURE 3 | Changes in the mean [HbO] of congruent condition in DLPFC **(A)**, FPA **(B)**, and VLPFC **(C)**. HbO, oxygenated hemoglobin; DLPFC, dorsolateral prefrontal cortex; FPA, frontal pole area; VLPFC, ventrolateral prefrontal cortex; PRE, before administration; POST, after administration. #Significant PRE vs. POST ($P < 0.05$). Values are mean ± SD.

sports. This discrepancy in results may reflect methodological differences related to the specific protocol used or the gender of the study participants. Moreover, we observed that high doses of caffeine had no effect on cognitive performance. One possible explanation for this finding is that the ingestion of high doses of caffeine induces side effects such as gastrointestinal upset, nervousness, mental confusion, and inability to focus (Graham and Spriet, 1995). Our data suggest that ingestion of low or moderate doses of caffeine ingestion decreases interference with successful performance on the Stroop task. As 3 mg/kg of caffeine improved performance on simple as well as complex cognitive tasks, we suggest that low-dose caffeine has a greater impact on cognition than moderate or high doses of caffeine.

Previous studies have reported the activation of the lateral prefrontal cortex (LPFC) upon execution of the Stroop task. Banich et al. (2000, 2001) suggested that LPFC activation may reflect interference processing and/or response inhibition. This may result in greater activation of relevant LPFC in the incongruent condition compared with the congruent condition. Milham et al. (2003) reported that during the Stroop task, the DLPFC in the LPFC is the primary region involved in the implementation of top-down attention control. Additionally, according to Krompinger and Simons (2011), the DLPFC resolves conflicts that occur during information processing of incongruent stimuli during the Stroop task. Therefore, the Stroop performance is more related to activation of the DLPFC. In the present study, we found a significant main effect of condition for the mean HbO of the DLPFC: the mean HbO in the incongruent condition was higher than in the congruent condition. These Stroop effect findings are similar to those in previous functional NIRS (fNIRS) studies, which suggested that executive functioning is associated with activation of DLPFC (Xu et al., 2017; Kujach et al., 2018). Interestingly, we found different results with previous two fNIRS studies (Xu et al., 2017; Kujach et al., 2018): the present Stroop task failed to activated the FPA and the VLPFC. But DLPFC activation in the present study is consistent with that of a previous meta-analysis review on Stroop task-related fMRI, in which FPA and VLPFC also could not be significantly activated (Nee et al., 2007; Huang et al., 2020). Thus, more fNIRS or fMRI neuroimaging studies are needed to clarify the roles of FPA and VLPFC in the Stroop task.

That caffeine improved the Stroop task performance may be related to activation of LPFC. Different from our hypothesis, caffeine ingestion failed to affect the mean HbO in the DLPFC, FPA, and VLPFC under the incongruent condition, whereas under the congruent condition, ingestion of 3 mg/kg of caffeine increased mean HbO in the DLPFC, FPA, and VLPFC. Combining the above-mentioned opposite pattern in which the mean HbO of DLPFC in the incongruent condition was higher than that in the congruent condition, indicated that mean HbO of LPFC, especially DLPFC, has been increased during Stroop-interference processing in the incongruent condition, whereas following caffeine ingestion, the significant reduction was found in the activation of LPFC. On the other hand, in the congruent condition, in which the cognitive processing is less demanding than in the incongruent condition, HbO of DLPFC has been less activated, whereas mean HbO in the DLPFC, FPA, and VLPFC was increased after the ingestion of 3 mg/kg of caffeine. These results demonstrate that under high cognitive processing, the effects of caffeine on LPFC activation have been attenuated by higher demanding processing, whereas under low cognitive tasks, the effects of caffeine on LPFC activation are more pronounced, because the congruent condition in Stroop task involved less demanding processing. The present results provide new evidences for previous studies that caffeine improvement of brain activation is induced more easily at the moment of the lowest values (Niioka and Sasaki, 2003; Souissi et al., 2019).

In the present study, under the congruent condition, no doses of caffeine ingestion affect the mean HbO. These results contrast with those of previous studies, which found that ingestion of 75 or 200 mg of caffeine was associated with decreased mean HbO on the Stroop task (Niioka and Sasaki, 2003; Dodd et al., 2015). This discrepancy in results may reflect methodological differences related to the specific protocol used. Therefore, use of the Stroop task should be standardized in future studies for investigating the effects of drugs on cerebral hemodynamic responses. Furthermore, under the congruent condition used, ingestion of 3 mg/kg of caffeine increased mean HbO in the DLPFC, FPA, and VLPFC. These results are consistent with those of a previous fMRI study, which showed that ingestion of low-dose caffeine enhanced neuro-activation in the frontal cortex (Diukova et al., 2012).

The increase in mean HbO during the Stroop task observed in this study after ingestion of low-dose caffeine may be related to an increase in regional cerebral blood volume (rCBV). Caffeine acts as an adenosine receptor antagonist and consequently as an excitatory neuro-stimulant, thus enhancing neural activity (Dunwiddie and Masino, 2001) and increasing rCBV. These findings are in line with a report by Higashi et al. (2004) that ingestion of 180 mg of caffeine maintained an increase in frontal rCBV during performance of an arithmetic task. Caffeine also regulates cerebral perfusion and acts as a vasoconstrictor, decreasing CBF via the blockade of A2A and A2B receptors (Laurienti et al., 2002; Pelligrion et al., 2010). Our observation that ingestion of low-dose caffeine increases mean HbO suggests that caffeine increases in rCBF via exciting neuro-stimulants outweigh caffeine decreases in rCBF via decreasing CBF. Along these lines, the lack of any observed effect of 6 or 9 mg/kg of caffeine on mean HbO suggests that, at these doses, the increase in rCBV may be equivalent to the decrease in CBF.

Moderate-to-high doses of caffeine administrated 1 h before and during exercise have been known to increase endurance athletic performance. In contrast, recent evidence has shown an ergogenic effect of low and extremely low doses of caffeine taken late during a period of prolonged exercise (Hogervorst et al., 1999; Jenkins et al., 2008). Furthermore, low doses of caffeine do not affect peripheral whole-body responses to exercise and are associated with few, if any, side effects; Spriet (2014) suggested that low doses of caffeine ingestion improve exercise performance In this study, we observed that ingestion of low-dose caffeine had greater effect on cognition and brain activation than had moderate and high doses, which means that low doses of caffeine have greater effect on stimulating the CNS. We suggest that ingestion of low-dose caffeine before and/or during exercise may induce more ergogenic effects than use of moderate or high doses.

Limitation

The present study maintained a few limitations. We used G-power to estimate the sample size, and the numbers of subjects in this study met the minimum sample size requirements. However, more samples are needed in the future research so that the research results can be further verified and repeated. In the double-blind designed study, it is best to ask subjects which dose they think they ingested in each trail after completion of all groups and to outline why they identified which trial as which. However, in the present study, we did not note the responses of the subjects, so we could not assess the efficacy of blinding.

Although four conditions in the present study are difficultly for participants to identify, we should value the assessment of blinding in future studies. Moreover, only Stroop task was used to measure executive function. There are other cognitive tasks on executive function, such as n-back and switching task. Therefore, more tasks are need to measure to ensure effects of various doses of caffeine ingestion on executive function in the future.

CONCLUSION

The present study found that ingestion of 3 mg/kg of caffeine improved performance on the Stroop task under both the incongruent and congruent conditions and increased mean HbO under the congruent condition. Ingestion of 6 mg/kg of caffeine improved performance on the Stroop task under the incongruent condition. These results demonstrate that ingestion of low-dose caffeine has greater effects on cognition and brain activation than moderate and high doses of caffeine, suggesting that low-dose caffeine may be a selective supplement in enhancing executive function and prefrontal activities.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study followed the ethical guidelines of the Declaration of Helsinki and was approved by the local Ethics Committee at the Shanghai University in Sport, Shanghai, China (No. 2016008). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XZ and YD conceived and supervised the study and designed the experiments. BZ and YL carried out the experiments. YL and XW analyzed the data. BZ wrote 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/fpsyg.2020.01393/full#supplementary-material

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The Effects of Acute Moderate and High Intensity Exercise on Memory

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Acute cardiovascular exercise can enhance correct remembering but its impact upon false remembering is less clear. In two experiments, we investigated the effect of acute bouts of exercise on correct and false remembering using the Deese–Roediger–McDermott (DRM) memory test. In Experiment 1, healthy adults completed quiet rest or moderate intensity cycling prior to the memory test. In Experiment 2, a similar sample completed moderate intensity running, high intensity sprints, or a period of quiet rest prior to the memory test. In Experiment 1, acute moderate intensity exercise increased short-term correct, but not false, recall. Experiment 2 replicated these findings but also found an acute bout of high intensity exercise had no impact upon either type of short-term recall. Acute moderate intensity exercise, but not acute high intensity exercise, can improve short-term correct recall without an accompanying increase in false recall potentially through processing of contextually specific information during encoding.

Keywords: acute exercise, exercise intensity, cognition, recall, recognition, false memory

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INTRODUCTION

Acute bouts of cardiovascular exercise provide moderate short-term post-exercise enhancements to several cognitive functions, including the speed of mental processing, attention, and executive function (see Chang et al., 2012; McMorris and Hale, 2012). These beneficial effects are associated with increases in arousal and available cognitive resources (e.g., Hillman et al., 2003), which are also proposed to be critical variables in efficient memory functioning. The influence of acute exercise on memory may depend on the temporal relation between the exercise bout, information encoding (the initial perceiving and learning of information), consolidation (memory trace stabilization into long-term memory formation after initial encoding) and subsequent recall (the retrieval of stored information). When exercise occurs immediately before a memory encoding task, there are moderate enhancements to the volume of studied information correctly remembered, whereas exercising during encoding appears to impair encoding (see Loprinzi et al., 2019, for a meta-analysis). Pre-encoding exercise is observed to be more beneficial than post-encoding exercise (Labban and Etnier, 2011), whilst concurrent exercise and encoding may impair subsequent recall (Soga et al., 2017). Furthermore, study characterizes in terms of exercise (intensity, duration), participants (age, fitness) and memory tasks (working memory, episodic memory, prospective memory) can moderate the potential for beneficial effects (Loprinzi, 2018). The majority of work has focused in correct recall, whilst little is known regarding acute cardiovascular exercise prior to either a short-term or long-term memory test can influence false remembering (memory of information that was not present at encoding).

Acute bouts of cardiovascular exercise, relative to rest, can enhance both short and long term explicit, declarative memory (memory that can be consciously recalled) of previously observed word lists. For example, enhancements have been observed after participants engaged in 10 min of brisk walking (e.g., English nouns: Salas et al., 2011), 40 min of moderate intensity aerobic cycling (e.g., English nouns: Coles and Tomporowski, 2008), six min of high intensity anaerobic sprints (e.g., Novel vocabulary: Winter et al., 2007), and 30 min of treadmill running above lactate threshold (e.g., Rey Auditory Verbal Learning Test: Etnier et al., 2016). In reviewing these patterns, when considering the type of memory task employed, Loprinzi (2018) suggests that whilst acute high-intensity exercise pre-memory task may impair working memory it can benefit episodic memory whilst high-intensity exercise post-encoding may not benefit long-term memory performance. These exercise-induced arousal memory benefits are thought to be associated with increased levels of brain-derived neurotrophic factor (BDNF) and catecholamines (dopamine, epinephrine, norepinephrine) (e.g., Winter et al., 2007).

The benefits of acute bouts of exercise on remembering may be of limited use if they are accompanied by increases in false remembering (e.g., recollecting events that did not happen or incorrectly recollecting events that did happen). To date, the impact of an acute bout of exercise on false remembering (as assessed using the DRM protocol) has only received limited examination. Green and Loprinzi (2018) found 15 min of self-paced brisk treadmill walking had no effect on correct or false declarative recall. Whilst Siddiqui and Loprinzi (2018) found that 20 min of brisk treadmill walking benefited accurate recall, with no differences in false recall. In contrast, Dilley et al. (2019) found 15-min high-intensity treadmill running (80%HRR) pre-encoding significantly increased correct recall over moderate intensity (50%HRR) exercise, the latter also enhanced memory over rest. False recall was not significantly impacted by exercise intensity, but the authors tentatively suggest their data indicates higher-intensity exercise may increase false recall. As such, the relationship between acute exercise pre-encoding warrants further consideration.

The Deese/Roediger-McDermott (DRM) paradigm (Roediger and McDermott, 1995) is widely used to induce false memories (see Gallo, 2010, for a review). Participants study lists of words (e.g., bed, dream, wake, snore, etc.) that are semantically associated with a non-presented critical lure word (e.g., sleep). In later assessment, participants frequently falsely recall and falsely recognize these critical lures as a previously studied word with high confidence. The Activation-Monitoring Theory (AMT, Roediger et al., 2001) and the Fuzzy Trace Theory (FTT, Brainerd and Reyna, 2002) explain why DRM word lists induce false memories. The AMT posits that, during encoding, the studied words (either consciously or unconsciously) activate the semantically associated critical lure. During subsequent memory tests, participants generate words based on their semantic activation at encoding. As the critical lure was activated at encoding, they commit a source-monitoring error and class it as a presented word (instead of an internally generated non-studied word). The FTT posits that participants generate two parallel memory traces (changes in the nervous system representing information) for studied words at encoding: verbatim traces (precise memory representations) and gist traces (vague meaning-based memory representations). The critical lures are strongly associated with gist of studied lists and are incorrectly presumed to have been studied. The AMT and FTT accounts are not mutually exclusive and both implicate the semantic association between studied lists and the non-studied critical lures in false remembering.

Currently, Loprinzi and colleagues (e.g., Siddiqui and Loprinzi, 2018) have tentatively suggested that moderate-intensity exercise may benefit accurate whilst reducing false declarative recall, whilst high-intensity exercise may elevate both accurate and false recall (Dilley et al., 2019). Consistent with this possibility, there is converging evidence from two distinct lines of research that self-reported arousal (admittedly, from other sources) can increase false remembering. Firstly, caffeine-induced arousal increased false recall of critical lures on memory tests (e.g., Mahoney et al., 2012). The second line of research demonstrates that high pre-encoding emotion-induced arousal can increase false remembering (e.g., Corson and Verrier, 2007). Taken together, self-reported arousal is often associated with increases in short-term memory false recall. Mahoney et al. (2012) and Corson and Verrier (2007) suggest that elevated arousal increases relational processing rather than item-specific processing at encoding in explain these effects. Item-specific processing focusses attention on individual studied items and how they are distinct from each other, whereas relational processing focusses participants' attention on the commonalities amongst studied items. Roediger et al. (2001) suggest that relational processing intensifies the spread of activation to the critical lures, which are more likely to be falsely remembered. These findings suggest some forms of arousal can increase false remembering and it is of interest to know whether this effect generalizes when the arousal is exercise-induced. For example, exercise-induced arousal (proposed to be associated with increases in neurotransmitters norepinephrine and dopamine) benefits speed of cognitive processing (McMorris and Hale, 2012).

The present within-subjects experiments examined the impact of a single acute bout of exercise on explicit, declarative short-term memory. Specifically, the effects of acute exercise undertaken immediately prior to encoding on subsequent short-term declarative correct and false remembering, as assessed via a DRM memory test. As exercise intensity, and therefore the degree of probable arousal, influences correct remembering, exercise intensity was manipulated here to see if it influences false remembering. More specifically, Experiment 1 examined whether engaging in an acute bout of moderate intensity aerobic exercise prior to encoding, relative to rest, impacts upon short-term declarative correct and false recall/recognition. Experiment 2 expanded this by examining whether engaging in acute moderate intensity aerobic exercise or high intensity anaerobic exercise prior to encoding, relative to rest, impacts upon short-term declarative correct and false recall/recognition. In both studies, it was anticipated that an acute bout of exercise prior to encoding would enhance short-term correct remembering. Despite previous findings (e.g., Green and Loprinzi, 2018), it is also tentatively predicted than an acute bout of exercise will elevate short-term false remembering as other forms of arousal (i.e., caffeine-induced, emotion-induced) are associated with increased false remembering (e.g., Corson and Verrier, 2007; Mahoney et al., 2012).

EXPERIMENT 1

Methods

Participants

Twenty six healthy and regularly physically active (>3 aerobic exercise sessions on three days per week for at least 30 min per session, >2 years of regular exercise participation) young adults (19M, 7F, Mage = 22.19 + 3.15 years) participated in the study after giving written informed consent. An *a priori* power analysis (using G*Power 3.1) with an α level of 5%, medium-to-large effect size (d = 0.6), and a power of 80%, based on effect sizes reported in previous within-subjects work (e.g., Etnier et al., 2016, N = 16; Labban and Etnier, 2018, N = 15) indicated that at least 19 participants would be required. All spoke English as their first language, had normal or corrected to normal vision, had no history of mood disorders, and were not taking any medication that would affect cognition. Participants were asked to refrain from strenuous physical exercise on the day of testing, to avoid caffeine and alcohol intake for 24 h prior to testing, to arrive appropriately hydrated, and to have not eaten for a minimum of 3 h.

Experimental Design

In a within-subjects design, participants completed two activities (rest or exercise) in a counterbalanced order. In the rest condition, participants were seated for 30 min prior to a DRM memory test. In the exercise condition, participants completed 30 min of moderate intensity exercise prior to a DRM memory test.

Activities and Measures

Rest Protocol

Participants were seated alone at a table in a quiet room and given the opportunity to read popular magazines for 30 min. This has been shown to be an acceptable rest activity the avoids boredom and does not impact memory function (Blough and Loprinzi, 2019). Participants were monitored to ensure they did not fall asleep or stand up and move around. Ratings of perceived exertion (RPE; individual's perceptions of exercise intensity) and affective valence (pleasure-displeasure) were recorded every two min.

Exercise Protocol

On a cycle ergometer (Monark, Model: 824E, Country: Sweden) participants completed a 5-min self-paced warm-up, followed by 30 min of moderate intensity cycling. Participants were asked to self-regulate a level of perceived exertion between *somewhat hard* and *hard* (within the 13–15 range on the Borg RPE scale), and were free to adjust their cadence to maintain their RPE within the target range. A reminder of the target RPE range was continuously in sight, and the researcher reminded participants every 2 min during exercise (offset from RPE measurement). RPE is a validated and practical perceptual method of directing self-selected exercise intensity, and this protocol has previously been used (e.g., Labban and Etnier, 2011) to ensure participants exercise at a moderate intensity below the ventilatory threshold. RPE, affective valence (pleasure-displeasure), and heart rate (HR) were recorded every two min. Water was available *ad libitum* throughout exercise.

Ratings of Perceived Exertion (RPE)

The Borg RPE scale (Borg, 1998) ranging from 6 (no exertion at all) to 20 (maximal exertion) was used to assess subjective interpretations of effort during exercise. The RPE scale is a widely accepted and validated method for estimating perceptions of exercise intensity, demonstrating high correlations (r = 0.80–0.90) between RPE and HR (Borg, 1998).

Affect

The Feeling Scale (FS; Hardy and Rejeski, 1989) is a single-item measure of pleasure and displeasure (how are you feeling right now?), 11-point bipolar rating scale ranging from + 5 (I feel very good), zero (neutral), to –5 (I feel very bad).

Heart Rate (HR)

Participants' HR was continuously monitored via a Polar Rate Monitor (Model A1; Polar Electro, Kempele, Finland) and recorded every 2 min.

Memory Task

The DRM paradigm (Roediger and McDermott, 1995) consisted of twelve lists of 15 word rated by Stadler et al. (1999) as producing high levels of false recognition (critical lures: Window, Doctor, Smoke, Anger, Cup, Slow, Sleep, Sweet, Rough, Soft, Cold, River). Participants were provided with standardized instructions on the task by the researcher, and this was repeated on the introductory computer screens. Two sets of 6 lists were assigned to each condition in counterbalanced order. Words were presented sequentially on a computer screen at a rate of 2s per word with a 1 s interval. Immediately after list, participants undertook a 1-min free recall test under the instruction to write as many words as possible using pen and paper. The number of correctly recalled old items (studied words), falsely recalled lures, and intrusions was totaled across the six lists. After the final free recall test, participants completed a 36-word recognition test similar to Knott and Thorley (2014). This test contained the six critical lures, 18 previously studied words (from positions one, five, and ten in each studied list), and 12 non-studied new words not semantically associated with the studied words or critical lures. On a paper response sheet, participants indicated whether the words were old (the word was previously studied) or new (the word was not previously studied). Old words were then rated as remember (recollect some contextual detail of seeing the word during encoding), know (recognized the word based on familiarity but had no recollection of any contextual information), or guess. Correct recognition of studied words, false recognition of critical lures, and incorrect recognition of non-studied new words (i.e., not critical lures) were calculated as proportions.

Procedure

Participants completed each condition activity (rest or exercise) individually on separate days at the same time of day in the same well-controlled laboratory setting led by the same researcher. There was a seven-day rest period between each session to control for factors that may affect memory performance (e.g., carry over effects). In the first session, participants read and signed an informed consent sheet, completed exercise readiness and health screening, and were familiarized with all equipment and testing procedures. On each day, participants first undertook the condition activity and then immediately completed the DRM memory tasks whilst seated in front of a computer in a distraction free testing booth situated next to the activity area. Upon completion of the activity, transition to the testing booth, reinstruction and commencing the memory task took approximately 2 min. A researcher was always present in the laboratory with the participant, and they provided the same instructions and monitoring to all participants. Following the completion of the final condition, all participants were debriefed about the aim of the experiment.

Statistical Analysis

Recall and recognition performance was analyzed with MANOVA followed by univariate ANOVAs using SPSS (version 22.0; International Business Machines Corp., Armonk, NY, United States), considering Condition (Rest vs. Exercise) as the within-subjects factor and word type (Recall: Critical Lure, Correct Recall, Other Error. Recognition: Critical Lure, Studied Word, New Word) as the dependent variables. If Mauchly's Test indicated sphericity was violated, a Greenhouse-Geisser correction was employed (εGG is reported in such cases). Partial eta-squared (ηp2) proportion of variance effect size was calculated and described with Cohen's (1988) cut-off points (i.e., small = 0.0099; medium = 0.0588; large = 0.1379).

RESULTS

Exercise Intensity

To check that the self-selected approach to targeting exercise intensity was successful, HR, RPE and Affect are assessed. The mean HR during exercise was 136 bpm (±17.34), indicating exercise was undertaken at an average of 68.40% of HRmax. The mean RPE reported during exercise was 12.65 (±1.23). Taken together, exercise was at a self-selected moderate intensity (Garber et al., 2011). Average affective responses were significantly more positive in the rest condition (3.38, ±1.81) compared to the exercise condition (1.71 ± 1.12), t (25) = 4.08, $p < 0.001$.

Short-Term Free Recall

The results showed a significant multivariate effect of Condition, $\lambda = 0.70$, $F(3, 23) = 3.28$, $p = 0.038$, $\eta_p{}^2 = 0.30$. The follow-up univariate analyses confirmed that the difference between Rest and Exercise was significant for Correct Recall (42.69 ± 9.21 vs. 39.35 ± 7.03), $F(1, 25) = 4.81$, MSE = 145.56, $p = 0.038$, $\eta_p{}^2 = 0.16$. Contrary to our tentative prediction, there was no significant difference in the number of critical lures falsely recalled in the exercise (2.69 ± 1.52) and rest conditions (2.08 ± 1.44), $F(1, 25) = 3.32$, MSE = 4.92, $p = 0.08$, $\eta_p{}^2 = 0.12$. There was no significant main effect of condition on other recall errors (2.88 ± 3.83 vs. 1.81 ± 1.90), $F(1, 25) = 0.89$, MSE = 3.25, $p = 0.35$, $\eta_p{}^2 = 0.03$ (see **Table 1**).

Recognition Memory

No significant multivariate effect of Condition on the proportion of words was recognized, $\lambda = 0.99$, $F(1, 25) = 0.17$, $p = 0.68$, $\eta_p{}^2 = 0.01$, nor Condition x Word Type interaction $\lambda = 0.99$, $F(1, 24) = 0.03$, $p = 0.97$, $\eta_p{}^2 = 0.02$ (see **Table 2**). Similarly, a MANOVA with Condition (Rest vs. Exercise) and Word Type (Studied vs. Critical Lure vs. New) as within-subjects factor, and judgment type (Remember, Know, Guess) as the dependent variables showed no significant multivariate effect of Condition on the proportion of words were recognized, $\lambda = 0.97$, $F(3, 23) = 0.24$, $p = 0.87$, $\eta_p{}^2 = 0.03$, nor Condition x Word Type interaction $\lambda = 0.91$, $F(6, 20) = 0.34$, $p = 0.91$, $\eta_p{}^2 = 0.09$. An equivalent, but large, proportion of studied words were recognized and critical lures falsely recognized in both conditions, whilst participants recognized few non-studied new words across conditions. Therefore contrary to expectations, exercise did not impact upon true and false recognition.

DISCUSSION

Experiment 1 demonstrated that acute moderate intensity aerobic exercise, relative to a period of rest, prior to a DRM memory task increased short-term correct recall. This is consistent with past research showing that exercise improves the ability to retain and recall information in short-term memory (Loprinzi et al., 2019). Contrary to expectations, participants' long-term correct recognition of studied words was equivalent regardless of whether they were tested after exercise or rest. Short-term correct recall and long-term correct recognition are, therefore, differentially impacted upon by exercise in this study. In a novel comparison, we also found that moderate intensity aerobic

TABLE 1 | Mean (SD) number of studied words correctly recalled (max = 90), critical lures falsely recalled (max = 6), and non-studied new words incorrectly recalled following two activities (rest or moderate intensity exercise) in Experiment 1.

Activity	Studied words	Critical lures	Non-studied new words
Rest	39.35 (7.03)	2.08 (1.44)	2.89 (3.82)
Exercise	42.69 (9.21)[a]	2.69 (1.52)	1.81 (1.90)

[a] *Significantly different from rest.*

TABLE 2 | Mean (SD) proportion of studied words correctly recognized, critical lures falsely recognized, and non-studied new items incorrectly recognized following each activity in Experiment 1.

		Rest	Moderate exercise
Studied Words	Old (*Correct*)	0.78 (0.12)	0.77 (0.19)
	Remember	0.38 (0.27)	0.44 (0.32)
	Know	0.27 (0.26)	0.25 (0.28)
	Guess	0.12 (0.17)	0.07 (0.06)
Critical Lures	Old (*Incorrect*)	0.87 (0.17)	0.87 (0.20)
	Remember	0.47 (0.34)	0.47 (0.34)
	Know	0.31 (0.28)	0.29 (0.30)
	Guess	0.09 (0.12)	0.11 (0.14)
New Words	Old (*Incorrect*)	0.19 (0.23)	0.17 (0.25)
	Remember	0.04 (0.07)	0.05 (0.12)
	Know	0.04 (0.09)	0.02 (0.07)
	Guess	0.11 (0.18)	0.10 (0.21)

exercise, relative to rest, has no impact upon number of critical lures (or other non-studied words) falsely recalled during a short-term memory test or falsely recognized during a long-term memory test. Supporting initial observations (Siddiqui and Loprinzi, 2018) this suggests exercise-induced arousal, unlike other forms of arousal (e.g., caffeine-induced, mood-induced) does not increase false remembering. It remains to be determined whether intensity can also influence false remembering. Furthermore, as the recognition test took place several min after the exercise had finished, it is unclear whether participants arousal levels had deteriorated in the exercise condition, so they were on par with those in the rest condition. If so, that could account for the null results. Experiment 2 therefore measures participants' arousal levels prior to and after each memory test.

EXPERIMENT 2

Experiment 2 compared the impact of rest, moderate intensity aerobic exercise, and high intensity anaerobic exercise on correct and false remembering as assessed via a short-term memory free recall test and a long-term memory recognition test. Consistent with several past studies (e.g., Winter et al., 2007), we used running protocols to elicit moderate and high intensity exercise. In methodological improvements to Experiment 1, we tailored the intensity in line with participants' individual fitness level.

Methods

Participants

Twenty-five healthy, normally functioning, and physically active males volunteered for the study ($M_{age} = 25.84 \pm 6.46$ years). Each had considerable prior experience of high intensity treadmill running. The inclusion, exclusion, and screening procedures were identical to Experiment 1. All participants were naïve to the aims of the study. Participants refrained from strenuous physical exercise on testing days, avoided caffeine and alcohol intake for 24 h prior to testing, and arrived appropriately hydrated, and having not eaten for a minimum of 3 h.

Experimental Design

In a within-subjects design modeled on that of Winter et al. (2007), participants completed three activities (rest, moderate intensity aerobic exercise, high intensity anaerobic exercise) in a counterbalanced order. In the rest condition participants rested for 40 min prior to a DRM memory test, in the moderate intensity exercise condition participants completed 40 min of steady state running prior to a DRM memory test, and in the high intensity exercise condition participants completed 2 × 3 min of sprints prior to a DRM memory test.

Activities and Measures

Rest Protocol

Similar to Study 1, participants sat quietly in the laboratory for 40 min and were given popular magazines to read, and were monitored throughout.

Exercise Protocols

Running was undertaken on a h/p/cosmos pulsar 3p treadmill (h/p/cosmos sports & medical GmbH). In the first testing session, participants' baseline fitness levels were assessed. In that session, participants completed a treadmill based graded exercise test to determine their VO2peak and HRmax. Oxygen uptake (VO2) was measured using a METAMAX cardiopulmonary exercise testing system (Cortex Biophysik GmbH) with breathing mask, pre-calibrated according to the manufacturer's instructions. A computerized indirect calorimetry system collected 30-s averages for oxygen uptake (VO2) and respiratory exchange ratio (RER). ***Moderate intensity exercise***: Participants completed 40 min of continuous moderate intensity running consisting of a 5-min warm-up (work rate at 30% of VO2peak), followed by 35 min of exercise at 60% of VVO2peak (Velocity at Vo2 Peak). ***High intensity exercise***: this condition aimed to achieve a very high intensity and high blood-lactate concentration (10 mmol/l or above) while limiting the total exercise duration, fatigue and dehydration. Participants completed a 5-min warm-up (30% of VO2peak), and then completed two incremental maximal efforts (3 min each), separated by 2 min passive recovery. In line with Winter et al. (2007) running protocol description, the treadmill speed started at 8 km/h, and increased every 10s by 2 km/h, until volitional exhaustion.

Heart Rate (HR), Affective Valence, Ratings of Perceived Exertion

These were measured in an identical manner to Experiment 1.

Arousal

Participants reported subjective arousal levels using 20-item Activation-Deactivation Adjective Checklist (ADCL), to generate four subscales; energy, tiredness, tension, and calmness. Participants rate affect adjectives on a four-point scale: definitely feel, slightly feel, cannot decide, definitely do not feel. The ADCL has acceptable reliability and validity (Thayer, 1989).

Blood-Lactate

Blood-lactate levels for moderate and high intensity running exercise was predicted to be above 10 mmol/l or below

2 mmol/l, respectively (Spurway, 1992). Blood-lactate was measured from fingertip capillary blood samples using an automated analyzer (Analox GM7 enzymatic metabolite analyzer, Analox instruments USA, Lunenburg, MA) immediately post-exercise and between recall and recognition tasks.

Memory Task

The DRM paradigm followed the same protocols from Experiment 1. Eighteen DRM lists of 15 words (critical lures: Window, Doctor, Smoke, Anger, Cup, Slow, Sleep, Sweet, Rough, Soft, Cold, River, Smell, Chair, Needle, City, Mountain, Spider) were divided into three sets of six and their assignment to each condition was counterbalanced. The recognition tests were constructed in a similar manner to Experiment 1.

Procedure

Participants individually attended four sessions (an initial screening and baseline fitness test, followed by the three activity conditions) on separate days at the same time of day (to control for diurnal variation) in the same laboratory. A seven-day rest period between each session controlled for fatigue and memory carry over effects. In the first session, participants read and signed an informed consent sheet, completed a pre-exercise health screening, the fitness test and were introduced to the memory task. In the second, third, and fourth sessions, the order of the three conditions were counterbalanced. To avoid dehydration, water was available *ad libitum* throughout exercise and participant were instructed to arrive hydrated. The same researcher provided the same instructions and monitored the participant during all activities and testing. Participants' RPE, affect, and HR were taken every 2 min during moderate intensity exercise and rest, and in the last min of each activity (sprint and recovery) of the high intensity condition. Immediately after each activity, a DRM memory test was completed in a distraction free testing booth situated next to the activity area. Upon completion of the activity, transition from the activity to the testing booth, reinstruction and commencing the memory task took approximately 2 min. A blood-lactate sample was taken and the ADCL was completed four times per experimental session: (1) before undertaking the activity (2) immediately prior to the free recall test, (3) immediately prior to the recognition test, and (4) after the recognition test. Following the final testing session, participants were debriefed regarding the aims of the experiment.

Statistical Analysis

Pre-activity blood-lactate, pre-activity arousal, average RPE, FS ratings, and HR were compared using one-way repeated measures ANOVAs. Post-activity blood-lactate was analyzed using two-way (Time × Activity) repeated-measures ANOVA. ADCL subscale ratings were analyzed using a MANOVA considering Condition (Rest vs. Moderate Exercise vs. High Intensity Exercise) and Time (Pre-Activity, Pre-free recall test, Pre-recognition test, and post-recognition test) as the within-subjects factor, and ADCL subscale (Energy, Calmness, Tiredness, Tension) as dependent variables. Mean number of studied words correctly recalled, critical lures falsely recalled, and non-studied new words incorrectly recalled in the three activity conditions was analyzed with a MANOVA followed by univariate ANOVAs, considering Condition (Rest vs. Moderate Exercise vs. High Intensity Exercise) as the within-subjects factor, and recall type (correct recall, critical lure, and other errors) as dependent variables. For the assessment of recognition, a MANOVA with Condition (Rest vs. Moderate Intensity Exercise vs. High Intensity Exercise) as the within-subjects factor and word type (Critical Lure, Studied Word, New Word) as the dependent variables was employed. If Mauchly's Test indicated sphericity was violated, a Greenhouse-Geisser correction was employed (εGG is reported in such cases). Partial eta-squared ($\eta_p{}^2$) is reported as a measure of effect-size.

RESULTS

Baseline Arousal and Blood-Lactate

There were no significant multivariate effect of Condition on participants' baseline arousal levels, assessed via the four ADCL subscales, prior to each of the three activities, $\lambda = 0.91$, $F(8, 90) = 0.53$, $p = 0.83$, $\eta_p{}^2 = 0.05$. Similarly, there was no significant difference in their baseline blood-lactate levels prior to each activity, $F(2, 48) = 2.63$, $p = 0.08$, $\eta_p{}^2 = 0.10$ (see **Table 3**).

End of Activity Exertion, Heart Rate, and Affect

RPE was significantly different in the final minute of each condition, $F(1.33, 31.96) = 108.57$, $p < 0.001$, $\eta_p{}^2 = 0.82$, εGG = 0.67. As would be expected, participants had significantly higher average RPE during high intensity exercise (16.36 ± 3.32) compared to moderate intensity exercise (12.68 ± 2.39; $p < 0.001$) and rest (6.12 ± 0.44; $p = 0.001$) conditions, and these latter conditions were also statistically different ($p < 0.001$). HR was also significantly different in the final minute of each condition, $F(2, 48) = 632.99$, $p < 0.001$, $\eta_p{}^2 = 0.96$, with high intensity exercise (170bpm ± 12.55, 88.04% HRmax) producing significantly higher average HR than both moderate intensity exercise (154.08 bpm ± 15.52, 79.43% HRmax; $p < 0.001$) and rest (66.12 bpm ± 7.34, 34.03% HRmax; $p < 0.001$). The latter two activities HR were also significantly different ($p < 0.001$). Affect was significantly different between conditions, $F(2, 48) = 17.48$, $p < 0.001$, $\eta_p{}^2 = 0.42$, with high intensity exercise inducing less positive affect (0.24 ± 2.52) than moderate intensity exercise (2.40 ± 1.76; $p < 0.001$) and rest (3.04 ± 1.67; $p < 0.001$). End of activity affect was equivalent for the latter two activities ($p = 0.59$). Finally, self-reported arousal in the final minute of each activity condition was significantly different, $F(2, 48) = 32.91$, $p < 0.001$, $\eta_p{}^2 = 0.58$. High intensity exercise (4.24 ± 1.56) induced average arousal levels significantly higher than moderate intensity exercise (3.32 ± 1.38; $p = 0.02$) and rest (1.92 ± 1.19; $p < 0.001$), which were themselves different ($p < 0.001$) (see **Table 4**). Combined, the above confirm that participants felt more exerted, aroused, and less pleasurable, in the final minute of the high intensity exercise than the moderate intensity exercise and period of rest. Moreover, they felt more exerted and aroused, but no less pleasurable, toward the end of the moderate intensity exercise than the period of rest.

TABLE 3 | Blood Lactate and Arousal responses (M ± SD) before and after the three activities (rest, moderate intensity exercise, high intensity exercise) in Experiment 2.

Measure	Time	Rest	Moderate exercise	Intense exercise
Blood Lactate mmol/l	Pre-activity	1.00 (0.41)	1.13 (0.42)	1.27 (0.45)
	Post-activity	1.08 (0.42)	1.78 (0.76)	6.20 (0.55)
	Post-Recall	1.01 (0.36)	1.74 (0.58)	6.22 (1.48)
	Post-recognition	0.96 (0.29)	1.51 (0.43)	5.60 (1.35)
Energy	Pre-activity	9.84 (4.09)	11.00 (4.93)	11.44 (5.08)
	Post-activity	7.88 (4.39)	13.40 (4.74)	15.36 (4.92)
	Post-Recall	10.12 (4.60)	10.80 (4.71)	10.00 (5.33)
	Post-recognition	9.96 (4.31)	9.96 (4.78)	10.36 (5.31)
Calmness	Pre-activity	14.08 (3.55)	13.60 (5.43)	13.04 (4.06)
	Post-activity	15.80 (5.26)	10.24 (3.32)	8.56 (3.92)
	Post-Recall	14.88 (5.87)	13.08 (5.34)	13.56 (3.92)
	Post-recognition	14.24 (4.87)	13.28 (3.92)	13.64 (4.21)
Tiredness	Pre-activity	9.12 (5.59)	8.52 (4.50)	8.60 (3.98)
	Post-activity	10.28 (5.73)	6.24 (3.36)	7.48 (6.47)
	Post-Recall	9.64 (5.18)	8.16 (4.90)	9.88 (5.15)
	Post-recognition	9.76 (5.44)	8.32 (4.71)	9.32 (5.48)
Tension	Pre-activity	7.44 (3.34)	7.76 (3.11)	7.68 (3.48)
	Post-activity	7.28 (2.85)	8.68 (3.04)	8.96 (2.26)
	Post-Recall	7.80 (3.23)	7.84 (3.47)	8.00 (2.69)
	Post-recognition	7.12 (2.99)	7.64 (3.60)	7.36 (2.38)

Post-activity Blood-Lactate

Our two-way analyses of post-activity blood-lactate levels revealed a significant main effect of Activity, $F(1.33, 31.94) = 283.78$, $p < 0.001$, $\eta_p^2 = 0.92$, εGG = 0.67. *Post hoc* analysis revealed that blood-lactate levels were significantly higher after high intensity exercise (6.01 ± 1.25 mmol/l) compared to moderate intensity exercise (1.68 ± 0.5 mmol/l; $p < 0.001$) and rest (1.02 ± 0.3 mmol/l; $p < 0.001$). Moreover, moderate intensity exercise resulted in higher post-exercise blood-lactate levels than rest ($p < 0.001$). There was also a main effect of Time, $F(1.24, 29.79) = 6.81$, $p = 0.002$, $\eta_p^2 = 0.22$, εGG = 0.62, indicating decreasing BL post-exercise. *Post hoc* analyses showed that blood-lactate levels were lowest Post-Recognition (2.69 ± 2.5 mmol/l) compared to Post-Exercise (3.02 ± 3.0 mmol/l; $p = 0.03$) and Post-Recall (2.99 ± 2.5 mmol/l; $p < 0.001$), which were themselves not different ($p = 0.12$). There was no Activity x Time interaction, $F(1.61, 38.74) = 1.55$, $p = 0.15$, $\eta_p^2 = 0.07$, εGG = 0.40. Together, this indicates exercise increased peripheral BL concentrations, and intense exercise resulted in the greatest elevation indicative of greater workload (see **Table 3**). However, whilst moderate intensity BL concentrations are in line with expectations, the intense anaerobic exercise did not reach the intended threshold (e.g., lactate levels above 10 mmol/l, Spurway, 1992).

TABLE 4 | During-activity RPE, HR (bpm), Affect and arousal (Mean ± SD) from final section of the three activities (rest, moderate intensity exercise, high intensity exercise) in Experiment 2.

Activity	RPE	HR (bpm)	Affect	Arousal
Rest	6.12 (0.44)[b,c]	66.12 (7.34)[b, c]	3.04 (1.67)[b,c]	1.92 (1.19)[b,c]
Moderate Exercise	12.68 (2.39)[a,c]	154.08 (15.52)[a,c]	2.40 (1.76)[a,c]	3.32 (1.38)[a,c]
Intense Exercise	16.36 (3.32)[a,b]	170 12.55)[a,b]	0.24 (2.52)[a,b]	4.24 (1.56)[a,b]

[a]*Significantly different from rest,* [b]*significantly different from moderate intensity exercise,* [c]*significantly different from high intensity exercise.*

Post-activity Arousal

The results showed a significant multivariate Condition x Time interaction, $\lambda = 0.58$, $F(24, 493) = 3.45$, $p < 0.001$, $\eta_p^2 = 0.13$. The follow-up univariate analyses confirmed significant Condition x Time interactions for Energy, $F(4.55, 109.17) = 13.67$, MSE = 108.74, $p < 0.001$, $\eta_p^2 = 0.36$, εGG = 0.76, Calmness, $F(4.02, 96.46) = 6.54$, MSE = 100.65, $p < 0.001$, $\eta_p^2 = 0.21$, εGG = 0.67, but not Tiredness, $F(3.42, 81.97) = 1.93$, MSE = 32.56, $p = 0.12$, $\eta_p^2 = 0.07$, εGG = 0.57, or Tension, $F(4.33, 103.96) = 1.14$, MSE = 5.40, $p = 0.34$, $\eta_p^2 = 0.05$, εGG = 0.72. Energy levels increased post-activity for both exercise conditions when compared to rest (which had reduced from baseline), these returned to comparable levels post-recall and recognition. There were lower calmness levels post-activity for both exercise conditions compared to rest (which increased from baseline), with the lowest calmness post-intense exercise. These returned to comparable levels post-recall and recognition, albeit with calmness remaining high for the rest condition. For Tiredness, there was a significant multivariate, $\lambda = 0.63$, $F(8, 90) = 2.89$, $p < 0.01$, $\eta_p^2 = 0.20$, and univariate, $F(2, 48) = 3.30$, MSE = 89.44, $p < 0.05$, $\eta_p^2 = 0.12$, effect of Condition. Bonferroni-adjusted pairwise comparisons revealed that Tiredness was significantly lower in the Moderate Intensity Exercise condition (7.81 ± 3.62) than Rest (9.70 ± 4.74, p = 0.02), but not High-Intensity Exercise (8.82 ± 4.63, $p = 0.59$). The latter two conditions were also not significantly different ($p = 0.84$). Taken together, both forms of exercise resulted comparable reductions in calmness and

TABLE 5 | Mean (SD) number of studied words correctly recalled (max = 90), critical lures falsely recalled (max = 6), and non-studied new words (not critical lures) incorrectly recalled after the three activities in Experiment 2.

Activity	Studied words	Critical lures	Non-studied words
Rest	42.20 (8.36)	2.68 (1.65)	1.52 (1.66)
Moderate Exercise	47.20 (7.43)[a]	2.64 (1.47)	2.28 (2.84)
Intense Exercise	45.16 (9.87)	2.84 (1.40)	1.96 (2.17)

[a] *significantly different from rest.*

increases in energy post-activity, which returned to baseline post-recognition (see **Table 3**). Tiredness was lowest during all phases post-moderate intensity exercise. There was a trend for larger effects of intense exercise on energy and calmness. Rest had a smaller, yet opposite effect on these characteristics.

Short-Term Free Recall

Table 5 shows mean number of studied words correctly recalled, critical lures falsely recalled, and non-studied new words incorrectly recalled in the three activity conditions. Results showed a significant multivariate effect of Condition, $\lambda = 0.76$, $F(6, 92) = 2.28$, $p = 0.042$, $\eta_p^2 = 0.13$. The follow-up univariate analyses confirmed a significant main effect of condition for Correct Recall, $F(2, 48) = 4.96$, MSE = 158.01, $p = 0.011$, $\eta_p^2 = 0.17$. As expected, Bonferroni-adjusted pairwise comparisons revealed that more studied words were correctly recalled after moderate intensity (47.20 + 8.36) exercise than rest (42.20 ± 8.36, $p = 0.005$). Contrary to expectations, there were no significant differences in the correct recall after moderate intensity and high intensity exercise (45.16 ± 9.87, $p = 0.52$) or after high intensity exercise and rest ($p = 0.39$). Importantly, the activity engaged in had no impact upon the number of critical lures falsely recalled, $F(2, 48) = 0.16$, MSE = 0.28, $p = 0.85$, $\eta_p^2 = 0.01$, or the number of non-studied new words incorrectly recalled $F(1.22, 46.33) = 1.82$, MSE = 37.92, $p = 0.19$, $\eta_p^2 = 0.07$ (Greenhouse-Geisser corrections applied to the latter main effect).

Recognition Memory

The mean proportion of studied words, critical lures, and non-studied new words classed as *old* following each of the three activities, and the proportion of *remember*, *know*, and *guess* made responses to these words, are in **Table 6**. There was no significant multivariate effect of Condition on the proportion of words correctly recognized, $\lambda = 0.86$, $F(1, 25) = 0.50$, $p = 0.80$, $\eta_p^2 = 0.14$. Similarly, A MANOVA with Condition (Rest vs. Exercise) and Word Type (Studied vs. Critical Lure vs. New) as within-subjects factors, and judgment type (*Remember*, *Know*, *Guess*) as the dependent variables showed no significant multivariate effect of Condition on the proportion of words were recognized, $\lambda = 0.82$, $F(6, 19) = 0.71$, $p = 0.65$, $\eta_p^2 = 0.18$. As such, despite large proportions of studied words being accurately and critical lures falsely recognized, and few non-studied new words being recognized, exercise did not impact upon true and false recognition rates.

GENERAL DISCUSSION

The current study provides initial evidence that acute aerobic exercise can not only enhance free recall performance, but also that this benefit is not accompanied by changes in false recall. In Experiment 1, results demonstrated that moderate intensity exercise improved free recall performance compared to a rest condition, with no associated increase in false recall. In Experiment 2, moderate intensity exercise again improved memory performance, and that this benefit was also observed compared to an intense exercise condition. The intense exercise condition, however, did not result in an increase in false memory recall. This partially supports and advances the initial observations made by Loprinzi and colleagues (Dilley et al., 2019; Green and Loprinzi, 2018; Siddiqui and Loprinzi, 2018) that exercise may have beneficial effects on false memory.

By assessing both free recall and recognition memory, the data suggests that whilst free recall was benefited, recognition memory was not influenced by exercise. This supports the Dilley et al.'s (2019) findings and may be due to the different mechanisms underlying free recall and recognition (Diekelmann et al., 2010). For example, recognition tasks aid source monitoring processes through the reactivation of sensory details of the study words and their encoding context (Cabeza et al., 2001) and recognition decisions are based on inferential judgments. This can be evidenced by the similarly high levels of critical lure recognition in both experiments, but otherwise low levels in the recall test. Also, recall tests were completed before the recognition test, which has been shown to influence recognition rates (e.g., Roediger and McDermott, 1995). Similar temporal considerations are important for the impact of exercise, as the effects of exercise on self-reported arousal and blood lactate had all decreased by the recognition testing phase, reducing the effects of exercise on response bias. However, given that exercise induced arousal was elevated during encoding, this requires further consideration.

In line with FTT, these findings suggest that exercise did not influence gist based memory processes when compared to quiet rest. Concerning the increased correct recall of presented words, exercise appears to have increased verbatim processing through focusing active attention on the perceptual details of presented words (potentially through effective mental rehearsal). This suggestion is in line with the proposal that acute moderate intensity exercise facilitates attentional allocation and efficient information processing speeds during cognitive tasks (e.g., Hillman et al., 2003; Kamijo et al., 2007), also evidenced through larger P3 amplitude (Hillman et al., 2003; Kamijo et al., 2007) and shorter P3 latency (Hillman et al., 2003). This improved active attentional allocation supported the encoding of contextually specific information, and consequentially assisted the recall of presented words but not non-presented words that were merely semantically activated. It is also possible that post-exercise encoding may inhibit automatic spreading activation. Given that arousal and BL levels were highest immediately post-exercise, it is likely exercise biased the encoding phase. Indeed, researchers suggest acute exercise may primarily benefit encoding rather than consolidation (stabilization of memory

TABLE 6 | Mean (SD) proportion of studied words correctly recognized, critical lures falsely recognized, and non-studied new items incorrectly recognized following each activity in Experiment 2.

		Rest	Moderate intensity exercise	High intensity exercise
Studied Words	Old (*Correct*)	0.84 (0.15)	0.85 (0.11)	0.84 (0.12)
	Remember	0.53 (0.25)	0.59 (0.59)	0.58 (0.24)
	Know	0.21 (0.24)	0.17 (0.19)	0.15 (0.22)
	Guess	0.10 (0.08)	0.09 (0.10)	0.10 (0.13)
Critical Lures	Old (*Incorrect*)	0.85 (0.18)	0.85 (0.21)	0.86 (0.22)
	Remember	0.52 (0.30)	0.59 (0.36)	0.53 (0.35)
	Know	0.24 (0.31)	0.15 (0.20)	0.24 (0.27)
	Guess	0.09 (0.14)	0.11 (0.17)	0.09 (0.18)
New Words	Old (*Incorrect*)	0.18 (0.24)	0.10 (0.24)	0.13 (0.13)
	Remember	0.03 (0.07)	0.02 (0.04)	0.05 (0.09)
	Know	0.01 (0.03)	0.03 (0.08)	0.02 (0.06)
	Guess	0.14 (0.23)	0.05 (0.09)	0.05 (0.08)

traces post-encoding) (e.g., Labban and Etnier, 2011), although others highlight exercise benefiting consolidation (McNerney and Radvansky, 2015). These initial findings point to a limited impact of physical exercise on false memory generation.

One key limitation is that no exploration of long-term memory consolidation processes is possible, which other researchers have highlighted as a key role of exercise (e.g., Tomporowski and Pendleton, 2018). There is also the potential that as the effects of exercise remain long after exercise completion, retrieval processes may also have been influenced by exercise. In addition, the present study did not take into account baseline in memory performance. This may be an important consideration given that both propensity for false recall (e.g., Diekelmann et al., 2010) and influence of exercise on cognition (e.g., Sibley and Beilock, 2007) are sensitive cognitive capacity.

Whilst the present study addressed exercise intensity, the protocols in terms of intensity and manipulation were not without issue. For example, the American College of Sports Medicine (2013) considers moderate intensity exercise to be between 64–76% of estimated HRmax. In Experiment 1, heart rates were well within this range (68.40% HRmax), yet participants in Experiment 2 exercised on average at 79.43%HRmax in the equivalent condition. This suggests that intensity may have been higher than expected in Experiment 2, and across the sample 13 participants were above this HR range. Using perceptual data, only 6 participants rated their RPE as being above the 13 upper limit identified as indicating moderate intensity exercise. Importantly, significant differences across all conditions in Experiment 2 for RPE and HR suggest that the conditions were distinct in terms of intensity. Yet a consequence is that across the experiments, moderate intensity exercise conditions were different not only in terms of intensity, but also the resultant affective experience. With Experiment 1 participants experienced moderate intensity exercise (RPE between somewhat hard and hard, with option to adjust intensity) as more positive than in Experiment 2 (intensity set at 60% of VO2peak). This may have been a result of the self-controlled nature versus prescriptive protocols employed, with self-selected exercise associated with more positive affective responses through perceived autonomy (Oliveira et al., 2015). Future research should explore the role of exercise intensity and its manipulation in terms of true and false memory generation. Finally, the generalizability of these findings are limited by the use of regularly physically active samples of young adults. Whilst there is limited evidence on the moderating role of fitness in the acute exercise and memory relationship (Loprinzi et al., 2019), fitness status is acknowledged an important consideration (Chang et al., 2012). Therefore, future studies are needed to explore the roles of exercise intensity and fitness, as well as other individual differences (e.g., cognitive capacity, age), proposed to moderate acute exercise and cognitive performance relationship.

In conclusion, the present study found that acute bouts of moderate intensity aerobic exercise performed before encoding and immediate retrieval of semantically associated words improved the volume of studied information correctly recalled. There were no associated increases in false memory generation, suggesting that exercise induced arousal facilitated verbatim memory traces rather than promoting gist-based processing at encoding. This is in line with Lambourne and Tomporowski (2010) meta-regression analysis observations that post-exercise exercise-induced arousal facilitates speeded mental process, as well as enhancing memory storage and retrieval, even if the exercise was intended to induce physical fatigue. This also supports initial proposals made by Loprinzi and colleagues (Green and Loprinzi, 2018; Siddiqui and Loprinzi, 2018; Dilley et al., 2019), and the encoding acute exercise benefits suggested by Labban and Etnier (2018). There may be a limitation to this arousal effect, as intense exercise did not result in improvements in free recall performance, potentially due to more negative affect during intense exercise compared to moderate intensity exercise. The beneficial effects may be associated with acute exercise's support of attentional processes and allocation, as well as arousal increasing verbatim processing of information. Research is required to address the underlying mechanisms and exercise characteristics (i.e., intensity, mode, duration and timing) that influence these false memory effects.

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 Edge Hill University Department of Sport and Physical Activity Ethics Committee. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DM, CT, and KM conceived, designed, and prepared the materials. DM and KM supervised the data collection. SH and LF collected the data. DM wrote the first draft. DM, CT, KM, SH, and LF contributed to the final approval of the version to be published and agreed to be accountable for all aspects of the work. All authors contributed to revising drafts critically for important intellectual content.

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Combined Factors for Predicting Cognitive Impairment in Elderly Population Aged 75 Years and Older: From a Behavioral Perspective

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To unravel the combined effect of risk and protective factors that may contribute to preserve or impair cognitive status, this prospective cohort study systematically investigated a cluster of factors in elders aged 75 years and older from Guangxi Longitudinal Cohort (GLC) dataset. GLC has tracked 630 oldest-elders for two times within 2 years and will continue to follow two times in the next 4 years. At baseline geriatric assessment, sociodemographic information (e.g., education, Mandarin, marriage, and income), physical status [body mass index (BMI), chronic disease/medicine], lifestyle factors (smoking, alcohol, and exercise), and self-rated mental health (self-care, well-being, anxiety) were recorded by online interview. With 2 years' follow-up, Mini-Mental State Examination (MMSE) and memory test were performed through person-to-person interview. The performance of MMSE was applied to represent the responder's cognitive status which classified into cognitive impairment and normal group based on a cutoff point of 20. An age-related cognitive declining trend of 15 stratified factors was observed, though with a small effect size (R-square: 0.001–0.15). The odds of exposure or non-exposure on factors (memory, self-care, exercise, income, education, and literacy) had a significantly different effect on cognitive impairment through multivariate analysis after adjusting other confounding variables. Through stepwise multiple logistic regression analysis, the following 12 factors/index would be integrated to predict cognitive impairment: gender, physical health factors (BMI, chronic disease), socioeconomic and lifestyle factors (education, literacy, Mandarin, marriage, income, and exercise), and psychological health factors (memory, self-care cognition, and anxiety). Related clinical and nursing applications were also discussed.

Keywords: cognitive impairment, protective/risk factors, elderly population, lifestyle, logistic regression

INTRODUCTION

Cognitive impairment, such as deterioration in memory, attention, and language, was considered as an inevitable trend of aging experienced by majority of elderly people (Folstein et al., 1985), the extent of which is strongly affected by individual variables (e.g., lifestyle, socioeconomic status) and their interactions. For someone, even the detail of experienced things could clearly be recalled, while some peers could not remember their own name. In current decades, the prevalence of cognitive impairment (e.g., mild cognitive impairment and dementia) has increased dramatically (Boyle et al., 2006) and considerable interest was attached in science research community (Deary et al., 2009). Taking China as an example, the estimated annual expenditures for cognitive impairment in the elderly population are predicted to be US$69 billion in 2020, which stressed a detrimental effect on family and other carers (Xu et al., 2017). As chronic and complicated characteristics, the effect of medical intervention to modify the course of cognitive impairment has not been effective and even hard to clearly attenuate impairment progression (Rocca et al., 2011). For cognitive impairment may be an agent of lifestyle-based causes, potentially modifiable behavioral factors are alternative to delay the onset of cognitive impairment (Friedman et al., 2015).

Accumulating epidemiological evidence indicates that psychological, environmental, and social factors can help to alleviate cognitive impairment and improve cognitive preservation (Wang et al., 2006; Rocca et al., 2011; Roberts et al., 2015; Arnau et al., 2016; Clare et al., 2017; Klimova et al., 2017; Lamblin et al., 2017; Zhang et al., 2017). A healthy lifestyle (refraining from smoking, moderate alcohol consumption, more physical activity/cardiorespiratory fitness, a Mediterranean-style diet, and more social and mentally stimulating activity) was associated with better cognitive performance and resilience (Hughes and Ganguli, 2009; Fung et al., 2011; Bielak et al., 2014; Dardiotis et al., 2014; Satizabal et al., 2016; Bubbico et al., 2019). Socioeconomic adversities (e.g., illiteracy, poor occupational achievement, and low income) could be potentially attributed to dementia (Scazufca et al., 2010). However, the measurements of these studies were heterogeneous with cross-sectional design and partial epidemiological factors. Comprehensive factors assessment and prediction were still lacking. Few studies have systematically examined the odds of the exposure and non-exposure of lifestyle factors. Moreover, exploring factors in a comprehensive and aggregated way would be a promising direction for preserving cognitive capacity. Thus, a systematic exploration of these factors is needed, and aggregately considering them was emphasized in current research. To collect factors in multiple level and as rich as possible, we classified the factors in lifestyle, socioeconomic, psychological, and physical aspect. Several pivotal modifiable factors associated with cognitive impairment will be refined after exploring the effect of each factor. The application for elder people and clinicians was suggested.

Besides, the diagnostic methods such as mild cognitive impairment (MCI) measurement were time-consuming and impractical for aging community survey (Rohrer et al., 2005). As a valid and brief tool of mental state assessment, Mini-Mental State Examination (MMSE, 30 items as well as 5–10 min testing time) covered a variety of cognitive competencies including orientation, memory, attention, reading, and writing with good identification property (Folstein et al., 1975). Here, the current study applied MMSE as a primary tool to measure cognitive impairment of elder individuals aged 75 years above. The aim of this study is to conduct a systematic analysis of factors and explore which is the best combination of protective and risk factors of cognitive impairment.

MATERIALS AND METHODS

Subjects

A total of 788 subjects with normal cognitive function aged 75 years and above were randomly collected at baseline based on census track in 13 communities according to Guangxi Longevity Cohort Project (GLCP). After 2 years' interval, the final sample consisted of 630 subjects (259 males, 371 females, mean age: 84.23) through interview in person (**Figure 1**). Subjects who died (81), not reached (30), and disconnected (47) were excluded from the following data analysis. The following participation rate was 80%.

Factors and Stratified Criteria

At baseline, multidimensional factors were collected in sociodemographic characteristics (gender, the number of children, marriage, income, education, and Mandarin), lifestyle factors (smoking, alcohol, and exercise), physical status [body mass index (BMI), eyesight, chronic disease/medicine], and self-rated mental health factors (self-care, well-being, and anxiety) through telephone interview. Subjects were asked questions such as: How do you think your well-being? Are you a smoker? How many cigarettes do you smoke per day? The interviewer recorded the answer in specific points based on the subject's response. All variables were stratified into two or four levels.

Sociodemographic Characteristics

Sociodemographic information was available regarding gender, age, up-bring children, education, Mandarin, and income. The number of children was divided as three children or more and less than three children. Marriage was classified as married and unmarried (including single, divorced, or widowed). Income grouped by more than 500 RMB and less than 500 RMB. Education was grouped as uneducated (never received education), less than 5 years, and more than 5 years. Mandarin was classified as capable (understanding and speaking Mandarin) and unable (cannot understand and speak Mandarin) groups.

Physical Health Factors

A brief measure of physical functioning was based on three separate tests of physical ability, regarding BMI (subject's weight in kilograms divided by the square of height in meters), eyesight, and chronic disease/medicine condition. Subjects whose BMI < 18.5 were taken as underweight, > 24 as overweight and range between 18.5 and 24 as normal. Eyesight was divided by normal (eyesight test < 1.0) and abnormal (eyesight test > 1.0) groups. Chronic disease/Medicine had two levels (taking, none) according to having chronic disease

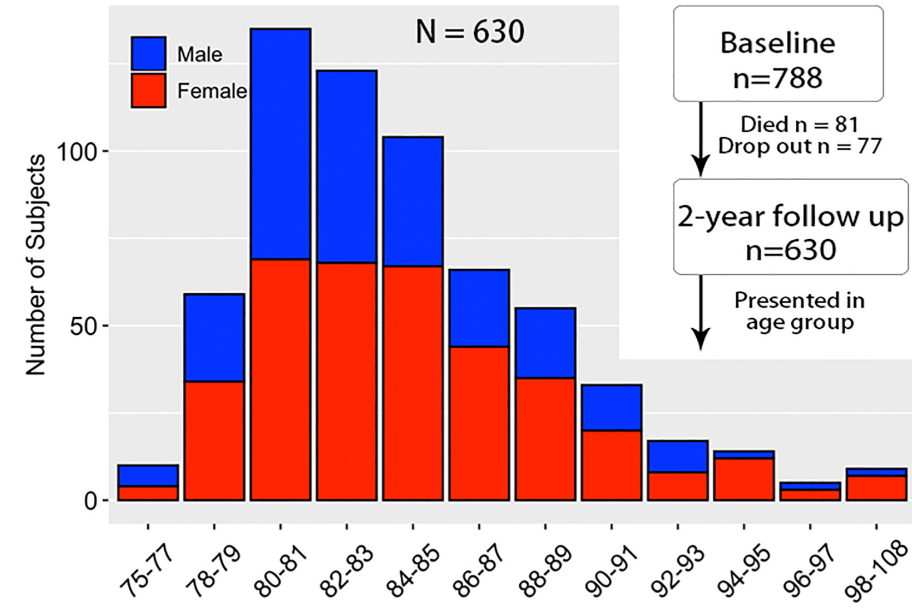

FIGURE 1 | Subjects age-group distribution and collection flowchart.

(like cardiovascular disease, respiratory disease) and taking medicines or not.

Lifestyle Factors

Smoking was classified as no smoking and smoking, whereas alcohol consumption was grouped into alcohol consumption and no alcohol consumption. Exercise was classified as > 50 min per day and < 50 min per day.

Self-Rated Mental Health

Self-rated mental health factors (anxiety, well-being, and self-care) were recorded by a single-item question with five alternative choices regarding excellent (receiving 5 points), very good (receiving 4 points), good (receiving 3 points), fair (receiving 2 points), and poor (receiving 1 point). Each specific component (like anxiety) was then divided into three stratified levels as low level (1–2 points), moderate level (3 points), and high level (4–5 points).

Follow-Up Assessment

With 2-year follow-up, the evaluation including two tests was conducted by coordinator interviewer in person. One test was MMSE (Molloy, 2014) as an index of cognitive status in which subjects are assigned into two groups, the cutoff point for the MMSE performance was 20. MMSE was commonly used to distinguish subjects into with and without cognitive impairment (Uffelen et al., 2008). MMSE score above 20 grouped into normal group, whereas score below 20 was treated as cognitive impairment group.

To validate the cognitive measurement, digit span test was utilized as supplemental cognitive measurement in addition to protective risk in which included 17 items (sequential memory: nine items; reversed order memory: eight items). Each item had 1 point if a subject gave a correct answer. According to the performance of the digit span task, memory was classified as four groups according to the sum of points: excellent (> 11.5), good (> 7.86), medial (≥ 4.2), weak (< 4.2).

In the spirit of collaboration and open science, the data are available for application and can be freely accessed at data sharing part in our lab web page: http://yanlab.club/index.php/info/128.html.

Statistical Analyses

All statistical analyses were performed in *Epicalc* (Chongsuvivatwong, 2007), an epidemiological data analysis tool in R. The data with missing records were omitted before statistical analyses. The function *lm* based on the least squares method was used to perform age-related linear modeling for each factor. The attributes of β (coefficients of the independent variables) and R-square (effect size) were calculated (**Figure 2**). Multivariate analyses using logistic regression models (*glm*) were conducted to identify the effect of exposure and non-exposure in specific factors on cognitive impairment in which crude odds ratio (OR) and adjusted OR (adjusted for other variables) were conducted (**Table 1**). Stepwise logistic regression (*step*) was followed for removing non-significant independent variables according to Akaike's Information Criterion (AIC) in which the optimal model with the lowest AIC value showed high likelihood or best fit. Specifically, the step removes each independent variable and compares the degrees of freedom reduced, the new deviance, and the

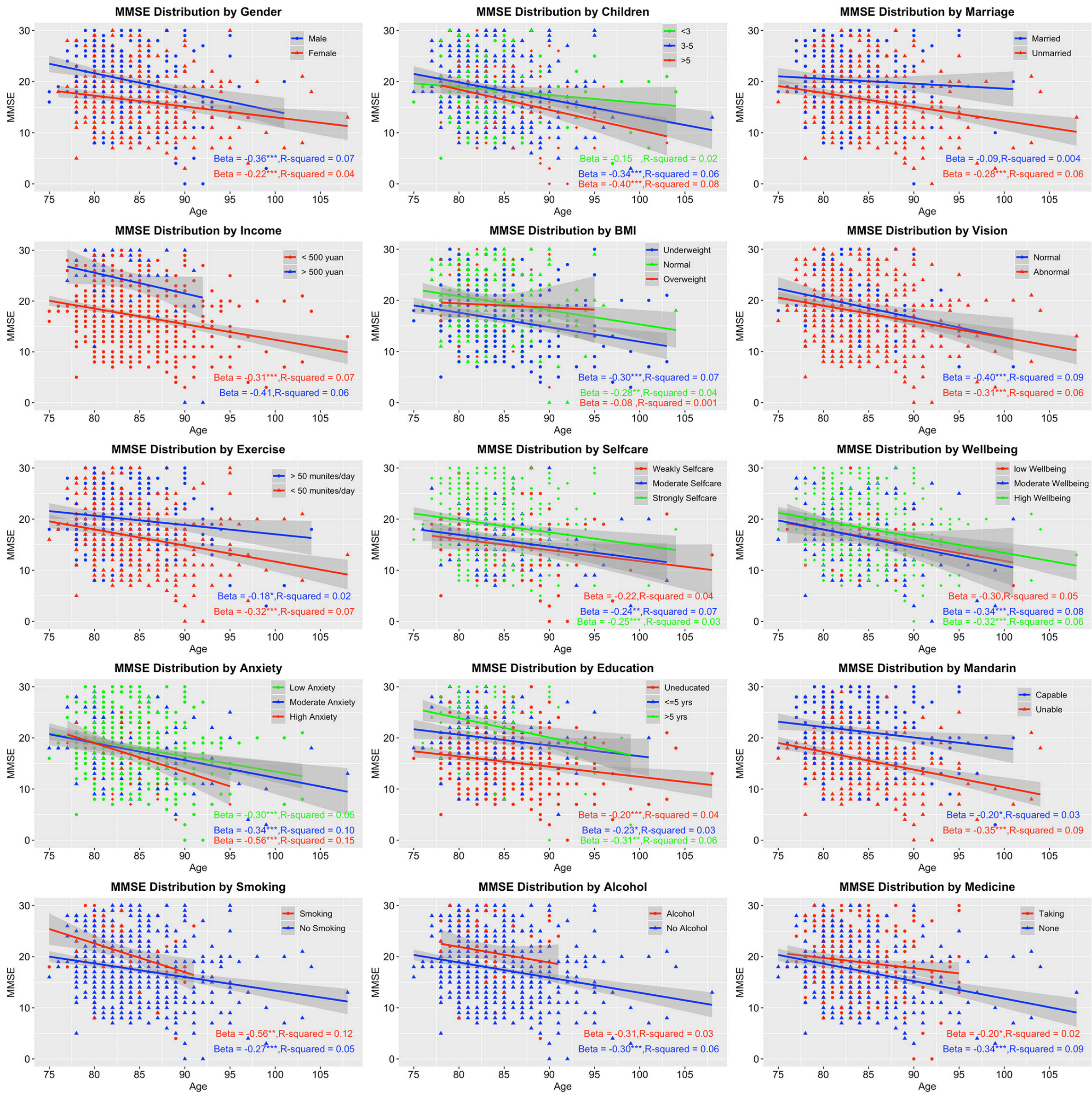

FIGURE 2 | Age-related trends of cognitive changes by stratified factors. The vertical axis presents Mini-Mental State Examination (MMSE) score symbolizing cognitive statue; the horizontal axis presents age. Beta (the strength of association) and R-square (effect size) of each stratified factor were also calculated. *p < 0.05; **p < 0.01; ***p < 0.001.

new AIC. The results are increasingly sorted by AIC. The top one having the lowest AIC is the best one (Step 6 in **Table 2**).

RESULTS

Age-Related Trajectories of Cognitive Changes via Stratified Factors

A linear declining trend was found in all factors stratified in two to four levels (**Figure 2**). Several factors showed stronger decreasing tendency such as high anxiety (β = -0.56) and smoking (β = -0.56), while others like married condition (β = -0.09) and overweight (β = -0.08) showed weaker associations. Unfortunately, all associations only reached small effect sizes (R^2 from 0.001 to 0.15).

The Effects of Exposure and Non-exposure in Specific Stratified Factors

In multivariate regression analysis on which the effects of exposure and non-exposure were checked (**Table 1**), the most significant factor that contributed to cognitive impairment was

TABLE 1 | The exposure and non-exposure effects of risk factors on cognitive impairment.

	Factors	Crude OR	95% CI	Adj. OR	95% CI	*p* (Wald's test)
Age	75	1.00				
	75 + 1	1.09	1.05–1.14	1.01	0.95–1.07	0.78
Gender	Male	1.00				
	Female	3.74	2.58–5.41	1.58	0.85–2.94	0.15
Children	0–2	1.00				
	> 3	1.01	0.66–1.55	1.11	0.58–2.10	0.75
BMI	Normal	1.00				
	Low-weight (< 18.5)	3.07	2.08–4.53	1.56	0.91–2.68	0.11
	Over-weight (> 24)	1.20	0.66–2.21	1.05	0.40–2.74	0.92
Self-care	Medial	1.00				
	Weak	0.63	0.28–1.44	0.22	0.07–0.70	0.01*
	Strong	0.23	0.11–0.43	0.21	0.09–0.50	<0.001***
Well-being	Medial	1.00				
	Weak	1.42	0.58–3.51	1.79	0.52–6.15	0.35
	Strong	0.74	0.46–1.18	1.26	0.63–2.52	0.52
Anxiety	Medial	1.00				
	Weak	1.02	0.64–1.65	1.76	0.89–3.49	0.10
	Strong	1.35	0.63–2.88	1.64	0.58–4.64	0.35
Education	None	1.00				
	1–5 years	0.21	0.13–0.32	0.77	0.38–1.55	0.46
	> 5 years	0.08	0.05–0.13	0.34	0.14–0.83	0.02*
Literacy	Literate	1.00				
	Illiterate	9.59	6.33–14.52	2.92	1.41–6.05	0.004**
Mandarin	Able	1.00				
	Unable	5.17	3.49–7.54	1.45	0.79–2.68	0.23
Marriage	Married	1.00				
	Unmarried	3.02	2.10–4.36	1.35	0.77–2.35	0.30
Income	Low (< 500 yuan)	1.00				
	High (> 500 yuan)	0.10	0.05–0.20	0.32	0.12–0.84	0.02*
Smoking	Smoking	1.00				
	Non-smoking	2.54	1.52–4.26	0.90	0.41–1.96	0.79
Alcohol	Drinking	1.00				
	Non-drinking	2.58	1.51–4.41	1.19	0.55–2.56	0.65
Chronic disease/	Taking	1.00				
Medicine	Never	1.51	1.06–2.15	1.26	0.74–2.13	0.39
Exercise	High (> 50)	1.00				
	Low (< 50)	2.50	1.74–3.58	3.10	1.80–5.31	<0.001***
Memory	Excellent	1.00				
	Good	6.14	3.27–11.56	4.84	2.25–10.39	<0.001***
	Medial	24.98	11.90–52.46	12.21	4.90–30.42	<0.001***
	Weak	55.05	21.00–144.30	36.78	11.62–136.44	<0.001***

*BMI, body mass index; CI, confidence interval. *p < 0.05, **p < 0.01, ***p < 0.001.*

memory. Compared to excellent memory subjects, five times increase in the odds of cognitive impairment, 12.21 times and 36.78 times for medial and weak memory subjects, respectively. Another significant mental health factor was self-care. Compared to medial level, weak level and strong level had only 0.22 and 0.21 times to developing cognitive impairment. Similarly, there are three sociodemographic factors that played as protective factors. As to non-education, subjects who received 1–5 years of education had only 0.77 times possibility resulting in cognitive impairment. If receiving education > 5 years, the odds decreased to 0.34 times. Similar to education, illiterate subjects had 2.92 times suffering cognitive impairment compared to literate subjects. Income is a representative index for subject's economic status, by which high-income subjects (> 500 yuan per month) had just 0.32 times led to cognitive abnormal referenced to low-income ones (< 500 yuan per month). Among lifestyle factors, the influence of physical exercise < 50 min/day had 3.1 times odds to lead to cognitive impairment compared to exercise > 50 min/day. Other factors did not show pronounced difference between exposure and non-exposure.

TABLE 2 | Crucial factors predicting cognitive impairment by stepwise regression.

	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Age	+	+				
Gender	+	+	+	+	+	+
Children	+	+	+	+	+	
BMI	+	+	+	+	+	+
Self-care	+	+	+	+	+	+
Well-being	+					
Anxiety	+	+	+	+	+	+
Edu	+	+	+	+	+	+
Literacy	+	+	+	+	+	+
Mandarin	+	+	+	+	+	+
Marriage	+	+	+	+	+	+
Income	+	+	+	+	+	+
Smoke	+	+	+			
Alcohol	+	+	+	+		
Chronic disease/Medicine	+	+	+	+	+	+
Exercise	+	+	+	+	+	+
Memory	+	+	+	+	+	+
AIC	457.08	454.04	452.12	450.22	448.36	446.58

BMI, body mass index; Edu, received education years; AIC, Akaike's Information Criterion, in which a low value shows a high likelihood or a good fit. Each column shows an alternative model, the model of Step 6 was found as the optimal model with the lowest AIC.

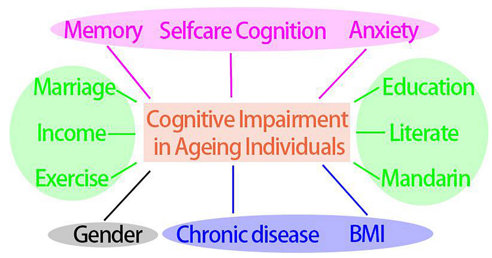

FIGURE 3 | Key potential modifiable factors that contribute to cognitive impairment in aging individuals. Blue ellipse: physical health factors, pink ellipse: psychological factors, green ellipse: socioeconomic and lifestyle factors, blank ellipse: generally unmodifiable factor.

The Aggregated Factors That Best Predict Cognitive Impairment

To check whether some crucial factors could combine to predict cognitive impairment as the optimal model, stepwise regression analysis was conducted (**Figure 3** and **Table 2**). The Step 6 was taken as the optimal model for which its lowest AIC value showed the best fitting results (466.58). The model encompassed Gender, BMI, Self-care cognition, Anxiety, Education, Literacy, Mandarin, Marriage, Income, Chronic disease/Medicine, Exercise, and Memory. Those factors may be more effective when they are combined to predict and intervene cognitive impairment for elderly populations aged 75 and older.

DISCUSSION

As lifestyle and other factors played an enduring and interacted way in the cognitive aging process, uncovering the protective or risk effect on cognitive impairment was a great challenge. Though numerous findings indicated that lifestyle and other sociodemographic factors impacted on cognitive performance (Mensink et al., 1997; Walsh, 2011; Roberts et al., 2015; Zhang et al., 2017; Clare et al., 2017), it is hard to explore the precise mechanism of each factor on cognitive change. Taking the determinants together would be a promising alternative to comprehensively consider protective or risk factors.

In the present study, a similar age-related decreasing trend of cognitive status was found in each stratified factor. Each factor independently contributed to cognitive impairment but with a limited effect size (Deary et al., 2009). Besides, a pronounced exposure effect was found in the following risks *via* multivariate regression analysis: lifestyle factor (physical activity/exercise), socioeconomic factors (education, literacy, income), psychological health factor (self-care cognition), and memory. Exposure in these factors made dramatically different chances to be onset of cognitive impairment. Taking memory as an illustration, the risks of cognitive impairment increased more than 36 times among weak memory individuals compared to that of excellent memory ones. It would be reasonable to infer that working memory stimulation tasks may be one of the most beneficial approaches for preserving and improving cognitive capacity in elder adults. A working memory intervention study also suggested that memory training was an effective way for maintaining normal cognitive function (Heinzel et al., 2014). As for other factors in the current study, low-level exercise (<50 min/day) responders had 3.1 times odds to suffer from cognitive impairment in comparison with high-level exercisers. It means that the value of physical activity was not limited in improving cardiovascular function but also can benefit psychological processes or brain health (e.g., delay cognitive decline) (Gregory et al., 2001). Regular fitness made great contribution to decreased mortality and morbidity rates (Gregory et al., 2001; Salmon, 2001; Uffelen et al., 2008). Other evidence also suggested that increased aerobic exercise was associated with structural and functional changes in elders' brain (Colcombe et al., 2006; Wei et al., 2014). Besides, other crucial sociodemographic factors such as education, literacy, and income also played a vital role in reserving cognitive status. Further evidence about their beneficial impact can be found in numerous aging studies (Perna et al., 2012; Calasanti, 2016; Livingston et al., 2017; Scarmeas et al., 2018).

Above all, as various causes led to cognitive decline in later life, exploring factors in an isolated approach was insufficient to explain cognitive impairment systematically. Instead, it would be appropriate to aggregate multifaceted factors into a unified profile. Only by doing so could clinical guidelines or healthy recommendation be efficient and appropriate, which was also suggested by review work (Plassman et al., 2010) from which a comprehensive consideration of risk and protective factors was necessary when drawing firm conclusions about associations with cognitive decline. The findings in the present study suggested that protective and risk factors were influenced by a number of potentially modifiable variables that could be targets for interventions to promote and reserve better cognitive function. Based on our analysis, the following four types including 12 factors/index would be considered to integrate for predicting cognitive impairment: gender, physical health factors (BMI, chronic disease), socioeconomic and lifestyle factors (education, literacy, Mandarin, marriage, income, and exercise), and psychological health factors (memory, self-care cognition, and anxiety). These potentially modifiable factors (gender excepted) showed promise in preserving cognitive capacity. Targeting these vital factors could help to reduce the incidence of cognitive impairment or substantially delay its onset (Colcombe et al., 2006). It would be constructive to encourage elder people using cognitive stimulation games/activities, like video games, playing cards, language learning, and so on, in which could enormously remedy deficiencies in education or literacy and improve well-being (Charness and Boot, 2009). Meanwhile, physical activity and psychological well-being are also recommended in nursing or clinical practice (McAuley and Rudolph, 1995; Ruuskanen and Ruoppila, 1995; McAuley et al., 2006). Taken together, each factor alone might manifest a spurious and faint association. A comprehensive considering those factors could be valid for predicting cognitive change and preserving cognitive capacity.

Besides, we did not observe significant associations between age and functional impairment. Previous study suggested that age was a major risk factor for cognitive decline (Deary et al., 2009). The reason may be the range of time in the current study was based on only 2 years, not a decade as a previous study (Guralnik et al., 1993). Therefore, the limited segment in our study would be insufficient to reflect the accumulated aging effect. Besides, the effects of smoking and alcohol drinking on cognitive decline were not found to be statistically significant, which was debated in previous evidence (Clare et al., 2017). Evidence was growing that moderate levels of alcohol intake may have a protective effect against dementia and cognitive decline compared with either abstinence or heavy drinking (Ganguli et al., 2005). Moreover, the crude dichotomous classification in our study might conceal the cognitive associations. More precise measurement according to actual consumption was necessary in future studies.

Several other limitations are also needed to be concerned carefully. Firstly, the subjects who participated in the present study came from a remote rural area of China. The external validity of cognitive status reduced and limited its generality. Also, an underestimated cognitive performance may occur for subjects who had relatively lower education and economic status than other older population living in an urban area. Thus, replicating investigation with larger samples and participants living in the city is necessary in future study. Secondly, we did not record information on genetic contribution, brain imaging evidence, healthy dietary habits, and emotional and social support factors, which have previously demonstrated associations with cognitive impairment (Dardiotis et al., 2014). Especially the related social factors, for social organizations are organism-like systems, such as in-group entitativity, which may play as a crucial protective factor for cognitive impairment and improve their life quality in terms of group support and well-being (Campbell, 1958; Pagliaro et al., 2013; Bubbico et al., 2019). Last but not least, we only utilized MMSE and digit span memory test as the measurement of cognitive function which limited the validation and generality of the results we found, though MMSE and digit memory test strongly associated and mutually confirmed the trends of cognitive aging process. Other objective measures, such as electrophysiological and brain imaging technologies, needed to address in future studies. More refined experimental design was also needed to make the protective and risk factors more valid and propel clinical application in cognitive aging field.

CONCLUSION

The comprehensive risk and protective effects of sociodemographic, lifestyle, and mental health on cognitive impairment were observed in subjects aged 75 years and older. We found an age-related declining trend of cognitive capacity in each stratified factor with slight diversity associations. The small effect size (R-square: 0.001–0.15) of individual factor suggests that a combined consideration of factors would be appropriate for clinical application and intervention.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Boards of Nanning Normal University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZY conceived the idea, designed the study, analyzed and interpreted the data, and drafted part of the manuscript. XZ and XH assisted with the analysis and interpretation of data. XZ conducted the experiment. All authors contributed to the article and approved the submitted version.

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Effects of Occupational Fatigue on Cognitive Performance of Staff From a Train Operating Company: A Field Study

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Background: Occupational fatigue is a key issue in the rail industry that can endanger staff, passenger, and train safety. There is a need to demonstrate the relationship between workload, fatigue, and performance among rail staff.

Objective: The present study, conducted in the workplace in realistic situations, integrating both subjective and objective measurements, aimed at demonstrating the relationship between workload, fatigue, and cognitive performance with a rail staff sample.

Methods: The "After-Effect" technique was applied in the current study. Online diaries and cognitive performance tasks were used to assess the fatigue, work experiences, and performance of rail staff before and after work on the first and last days of one working week.

Results: Reported fatigue was greater after work on both the first and last day of the working week. There were large individual differences in the change in fatigue and workload ratings. Analysis of covariance with age and the pre-work performance score as covariates and the post-work performance score as the dependent variable showed that high levels of fatigue were associated with impaired performance on both the visual search and logical reasoning tasks. Workload had fewer effects on performance than fatigue.

Conclusion: This field study provided evidence for the relationship between work-related fatigue and performance impairment. The findings show the need for future work on predicting fatigue-related performance decrements, and the necessity of providing interventions and support so that the risk to safety can be reduced.

Keywords: occupational fatigue, rail industry, rail staff, field study, performance

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INTRODUCTION

Fatigue is often an indicator of an unhealthy lifestyle. It has found to be associated with higher probability of illness and injury in the workplace (Harma et al., 1998, 2002; Chau et al., 2008). Fatigue is synonymous with a generalized stress response over time. Occupational fatigue may occur during or after work; it may also occur before work when the worker has not fully recovered from previous fatigue through the regular periods of rest before the onset of the next set of demands (Cameron, 1973). It has been found to be associated with impaired cognitive performance, including increased reaction time, decreased vigilance, perceptual and cognitive distortions (reviewed in Krueger, 1989), dropped skill effectiveness (Drew, 1940). Fatigue also leads to impaired memory and information processing (Craig and Cooper, 1992), reductions in concentration, motivation, and activity (Beurskens et al., 2000). In addition, fatigue may impair the sense of agency (i.e., the loss of the sense of being responsible for own's actions; Howard et al., 2016), which increases the safety risks in the workplace. In particular, previous studies show that human agency was reduced by increased out of the loop events which could be associated with fatigue, and decreased control or increased automation in the environment (Berberian et al., 2012; Kumar and Srinivasan, 2012, 2013; Moore, 2016; Di Plinio et al., 2019, 2020). Such effects may also show inter-individual differences (Di Plinio et al., 2019) and also vary with cultural background (Barlas and Obhi, 2014).

In the railway industry, occupational fatigue is a severe problem which jeopardizes not only the staff health but also train and passenger safety, as most jobs are safety-critical. Evidence for fatigue among rail staff has been found in previous studies, in which various methods have been used, including surveys (Cotrim et al., 2017; Fan and Smith, 2017), incident reports (reviewed in Buck and Lamonde, 1993; Ugajin, 1999; Fan and Smith, 2018), simulated driving studies (Dorrian et al., 2007), and interviews (Filtness and Naweed, 2017). In particular, fatigue is considered to be a causal or contributory factor in the majority of train accident and incident investigation reports (British Rail Safety and Standards Board, 2005; British Rail Accident Investigation Branch, 2008, 2010). Fatigue, its impact on task performance, and fatigue-related human errors have been found in previous research in several different transport sectors (e.g., road drivers: Feyer and Williamson, 2001; seafarers: Smith et al., 2006), and has also been suggested as a key issue for train safety (Bowler and Gibbon, 2015). However, the field of rail fatigue research was historically smaller than that of other transport sectors, and the investigation of the effect of fatigue on performance in real time in the workplace is still lacking in this industry.

The causes of occupational fatigue can emanate from either inside or outside the workplace, and mainly include task-related factors and sleep-related factors. Jobs in the rail industry were designed to operate on a 24/7 basis, often with an irregular schedule. A large-scale study (Fan and Smith, 2017) identified the main predictors of fatigue in the rail industry as high job demands (i.e., workload), shift-work, poor job control and support, and noise and vibration in the working environment. Shift work, especially the night and early morning shifts, disrupts the sleep–wake cycle (Ferguson et al., 2008) and deprives workers of sleep (Åkerstedt, 1991). Shift workers have little time to recover when working certain shift hours, which makes them more likely to suffer from cumulative fatigue (Åhsberg et al., 2000). Moreover, Dorrian et al. (2011) indicated that in addition to work hours and sleep length, workload significantly influenced fatigue among train crew. It is notable that mental workload is the major problem in the modern railway industry rather than traditional physical workload, due to the increasing level of automation in operating systems (Young et al., 2015; Fan and Smith, 2019). The majority of job tasks in this modern industry require more cognitive demands (e.g., selective attention, sustained vigilance), resulting in a heavy mental workload and increased fatigue; meanwhile, fatigue is associated with a deterioration of attention and impaired performance. Failure to maintain such performance at an acceptable level brings danger, especially to those working in safety-critical job roles.

Subjective measurement of fatigue has been validated as a reliable way to distinguish between fatigued and non-fatigued staff (e.g., Chalder et al., 1993; Kim et al., 2010), and this is widely used in different types of job disciplines, both within (Kishida, 1991) and between industries (Kogi et al., 1970; Beurskens et al., 2000). Recently, however, Cheng and Hui-Ning (2019) argued that the ability of rail staff to perceive their own fatigue could be limited, which may due to sleep debt and cumulative sleep loss, particularly following a string of atypical shifts (night or early morning shift). Therefore, it is important to also include objective measurement of fatigue and performance which can be used in the work situation along with subjective measurement to reducing potential subjective biases. However, it can be a challenge to apply certain objective measurements in the railway environment. Railway companies usually have their own rules regarding staff uniforms for consistency and safety, which means that wearing extra instruments for objective measurement, such as Electroencephalography (EEG) or eye-tracking equipment, is not allowed in the workplace, as it may cause distractions and other potential safety risks.

Broadbent (1979) suggested that using the "After-Effect" technique in fatigue measurement could be applicable in realistic situations. This involves measuring performance before and after a specific task or work period, without changing people's normal behaviors during and after the task. The after-effect symptoms of fatigue usually include longer reaction times and reduced accuracy. In the work context, the After-Effect method compares the difference in performance before and after work, and a greater difference reflects a greater effect. This method has already been widely used in workload studies (e.g., Parkes, 1995; Hockey and Earle, 2006). For instance, workload study Parkes's (1995) found that reaction time and accuracy in search tasks and logical reasoning ability showed clear impairments due to the effect of higher workload. It has also been used to assess other factors which contribute to fatigue, such as the common cold (Smith et al., 2000), caffeine (Brice and Smith, 2001; Smith, 2002; Doherty and Smith, 2005), and night work (Åkerstedt, 1988). Recently, Smith and Smith (2017) used the After-Effect method to assess rail engineers' fatigue and performance on the first and last day of the work week and showed that the extent of fatigue could be identified using this methodology.

Online fatigue measures could be a more appropriate tool for detecting fatigue in the workplace due to their convenience and low development cost. Online cognitive tests have been used for the past two decades, and a review of them confirmed their ability to provide realistic simulations of cognitive tasks in daily life, which is the main advantage of computerized cognitive evaluation (see Crook et al., 2009). It is possible for online measures to be used in the workplace and they are often more convenient than offline tests or the use of measures from laboratory experiments. One fatigue study with students, which used a methodology that combined the After-Effect method and online cognitive performance tasks to measure fatigue in a real-life setting (Fan and Smith, 2017), established the relationship between workload, fatigue, and cognitive performance. This study showed that workload increased subjective fatigue after work which then resulted in cognitive performance impairments, including slower reaction time and decreased accuracy, while the effect of time of day on performance was not found significant. However, this study consisted of undergraduate students with risk factors for fatigue due to their study life at university, which are different from fatigue in the actual work life of the railway industry. Thus, a further experiment based on a staff sample is needed.

The present study aimed to use this same methodology to demonstrate the relationship between workload, fatigue, and objective performance with staff from a train operating company. The company was interested in generic fatigue across a range of jobs. Other research has adopted the present approach to study train drivers (Evans, 2019), conductors, guards, and engineers (Smith and Smith, 2017). The methods used in this study consisted of a self-assessment diary, mainly used to record ratings of fatigue and workload, and also objective performance tests. The experimental hypothesis for this study predicted that an increased feeling of fatigue would lead to performance reduction, including delayed reaction time, and lower accuracy rates in both visual search and logical reasoning tests. This methodology was also used to examine whether the effects of fatigue and workload were different.

MATERIALS AND METHODS

Participants

This study recruited participants with different types of jobs from volunteers from a train company in the *United Kingdom* [$N = 19$, mean ($\pm$ SD) age = 41.86 $\pm$ 9.89 yrs.; 74% male], as all job types may be susceptible to fatigue (Fan and Smith, 2017). The main job types reported were managers, conductors, drivers, station workers, engineers, and administrators. Selection of different job types meant that any obtained results could be generalized across occupations. Participants were fit for work but no other data was collected on health status.

Procedure

This study included four sessions in total, requiring participants to complete the diary and the tests immediately before starting work, and immediately after finishing work on the first and fourth days of a working week. For example, if one participant was off-work on Tuesday and Wednesday, and then worked the following four continuous days, this participants would complete the diary on Thursday (the first day of his or her working week) and on Sunday (the last day of his or her working week). An invitation e-mail with attached information about the study and an informed consent form was sent to potential participants. Once participants had signed and returned the forms, they were asked to provide the start date of their next work week with four continuous days of working. The links to the four test sections and a familiarization session were then sent to them. The familiarization session included an introduction to the diary and an example of each cognitive task to ensure that the participants were able to complete the tasks correctly before starting the study. On the testing day(s), participants were asked to complete the online diary and cognitive tasks immediately before starting work and immediately after finishing work via a computer or mobile phone.

Participants were free to withdraw from the survey at any point. This study was reviewed and approved by the School of Psychology Research Ethics Committee at Cardiff University and carried out with the informed consent of the volunteers.

Materials

The materials used in this study included a diary and two online cognitive tasks and took about 15 min to complete. These online measures required assessment by mobile phone or computer, and participants responded by touching the screen (if using mobile phone) or clicking on the mouse (if using the computer). All the tasks and data collection were via the Qualtrics online survey platform.

Diary

The diary was used to measure fatigue and the causes of fatigue. It consisted of 15 single-item questions, including six questions to be answered before work and nine questions to be answered after work. **Supplementary Table 1** (in **Supplementary Material**) shows the details of the diary questionnaire. It was designed based on the material used in Smith and Smith's (2017) diary studies, and majority questions were on a 10-point scale. The questions in the pre-work diary covered sleep duration and quality, commute time, fatigue due to the commute, general health status, and alertness before starting work. The questions in the post-work diary recorded workload, effort, fatigue, stress, break duration, work duration, time of work completion, and level of distraction during work. There were extra questions in the post-work diary on the last day, which asked whether the participants had worked at the same time every workday during the working week; if participants answered no, they were asked about their working time for each day.

Online Cognitive Tasks

Two online cognitive tasks were used to assess objective performance in each session: a visual search and a logical reasoning task. These two tests have been widely used in previous workload (e.g., Parkes, 1995) and fatigue studies (e.g., Lamond and Dawson, 1999; Barker and Nussbaum, 2011). The online version of such tests was validated in our previous study with the student sample (Fan and Smith, 2017; Fan, 2019). **Supplementary Figures 1**, **2** (in **Supplementary Material**) shows the example of a trial of each task. For both tasks, the inter-trial intervals were 500 ms. The tasks were distributed and the data collection was completed via the Qualtrics online survey platform. Participant would assess the task using either computer or mobile phone, responding by clicking mouse or tapping touch screen.

The visual search task consisted of 12 trials, which randomly appeared from a total of 30 possible trials. In each trial, participants were randomly shown a 60-letter set and one target letter. They were required to find and click the target letter as quickly and accurately as possible on the screen. The response time and accuracy for each trial were recorded.

The logical reasoning task consisted of 24 trials and required the participants to make a decision between two options as quickly and accurately as possible. This test was based on Baddeley's (1968) grammatical reasoning test. The outcome measures were response time and accuracy.

ANALYSIS

Both the diary and the cognitive tasks were presented online using the Qualtrics software package. The diary and performance data were then downloaded into a single SPSS data file. Analysis was carried out using the IBM SPSS 25 package. The main focus of the analysis was on the associations between fatigue and workload and changes in performance over the day. Analyses of covariance with the pre-work measures and age as covariates, and the post-work performance scores as dependent variables were carried out. Fatigue and workload change scores were split into high and low groups (based on the median of scores from these questions in the diary) and these were the between subject factors in the analyses of covariance. Fan and Smith (2017), in a study of university students, found that fatigue reduced visual search accuracy and led to slower logical reasoning speed. Workload had no significant effects. One-tail significance levels were used where the two tailed level was not significant, as it was predicted that high fatigue and high workload would be associated with impaired performance seen in the Fan and Smith (2017) study.

RESULTS

The Sample

Nineteen participants, 14 of whom were male, completed the whole study. The most common job types reported were managers (26.3%), engineers (15.8%), conductors (15.8%), drivers (15.8%), and station workers (15.8%), followed by administrators (10.5%). Most participants did daytime shifts (68.4%), while 31.6% did night shifts (begin between the hours of 7:00 p.m. and 12:00 a.m.) or early morning shifts (begin between the hours of 12:00 a.m. and 6:00 a.m.). Nearly half (43.1%) of the participants worked two or more different shift times during the testing week (4 days).

Fatigue and Workload Ratings

The descriptive statistics for the fatigue ratings and the performance tasks, are shown for pre-work and post work on the first and last day of the working week in **Table 1**.

On the first working day, fatigue ratings showed a large increase over the day (pre-work mean = 2.16; post-work mean = 6.42). There was considerable variation across individuals with the increase in fatigue having a range from 0 to 800%. A similar profile was seen for the last working day (pre-work mean: 2.47; post-work mean = 7.11), and again there were large individual differences in the change of fatigue over the day (range = −14–900%). Workload ratings were consistent across days (Day 1: mean = 5.79, SD = 2.18; Day 4: mean = 5.42, SD = 2.43) and showed large individual differences (Day 1: range = 1–9; Day 4: range = 1–9).

Changes in fatigue over the day were correlated with age (Day 1: $r = 0.73$, $p < 0.001$). On the last day increased fatigue was associated with greater distraction due to thinking about other things ($r = 0.49$, $p < 0.05$). Workload ratings were associated with ratings of effort ($r = 0.61$, $p < 0.01$), stress ($r = 0.49$, $p < 0.05$), and alertness ($r = -0.49$). These results show that fatigue and workload are different constructs which are only weakly correlated.

Changes in Fatigue, Workload and Performance Changes Over the Day

Analyses of covariance were carried out to examine associations between changes in fatigue, workload and performance after work. Changes of fatigue and workload were divided into high and low groups using a median split. Before work performance measures were covariates for the corresponding after work measure (the dependent variable). Age was also included as a covariate. It was predicted that increases of fatigue and workload would be associated with impaired performance.

On the first day, the high fatigue group had less accurate performance on the visual search task than the low fatigue group ($F = 3.78$, df = 1.13, $p = 0.037$, 1-tail, partial eta squared = 0.225). This result is shown in **Figure 1**.

Also on Day 1, the high workload group had less accurate performance on the logical reasoning task than the low workload group ($F = 5.37$, df = 1,13, $p = 0.037$, partial eta squared = 0.292). This result is shown in **Figure 2**. None of the other effects were significant.

On the last working day, the high fatigue group again had less accurate performance on the visual search task ($F = 5.84$, df = 1,13, $p = -0.031$, partial eta squared = 0.310). This is shown in **Figure 3**.

The high fatigue group were also slower than the low fatigue group on the logical reasoning task on the last day ($F = 3.38$, df = 1,13, $p < 0.045$, 1-tail, partial eta squared = 0.206). This is shown in **Figure 4**.

DISCUSSION

The present research involved a field study using online fatigue tests integrating both subjective and objective measurements, which was validated in a previous fatigue study (Fan and Smith, 2017). The design of the fatigue tests combined online methods and the After-Effect technique. This methodology was suitable and convenient to use in the workplace, especially in the railway industry where wearing

TABLE 1 | Descriptive statistics for fatigue ratings and performance tests (mean [SD]).

	Day 1 Pre-work	Day 1 Post-work	Day 4 Pre-work	Day 4 Post-work
Fatigue ratings (scale of 1–10; high scores = greater fatigue)	2.16 [1.21]	6.42 [2.12]	2.47 [1.61]	7.11 [2.00]
Visual search accuracy (% correct)	97.81 [4.68]	97.81 [4.68]	94.07 [5.77]	90.35 [8.45]
Visual search speed (s)	13.58 [3.15]	14.25 [3.00]	13.93 [3.54]	14.29 [3.06]
Logical reasoning accuracy (% correct)	74.34 [20.00]	77.63 [21.35]	74.78 [22.27]	79.39 [23.63]
Logical reasoning speed (s)	6.28 [1.73]	6.94 [2.39]	5.58 [1.40]	5.66 [1.38]

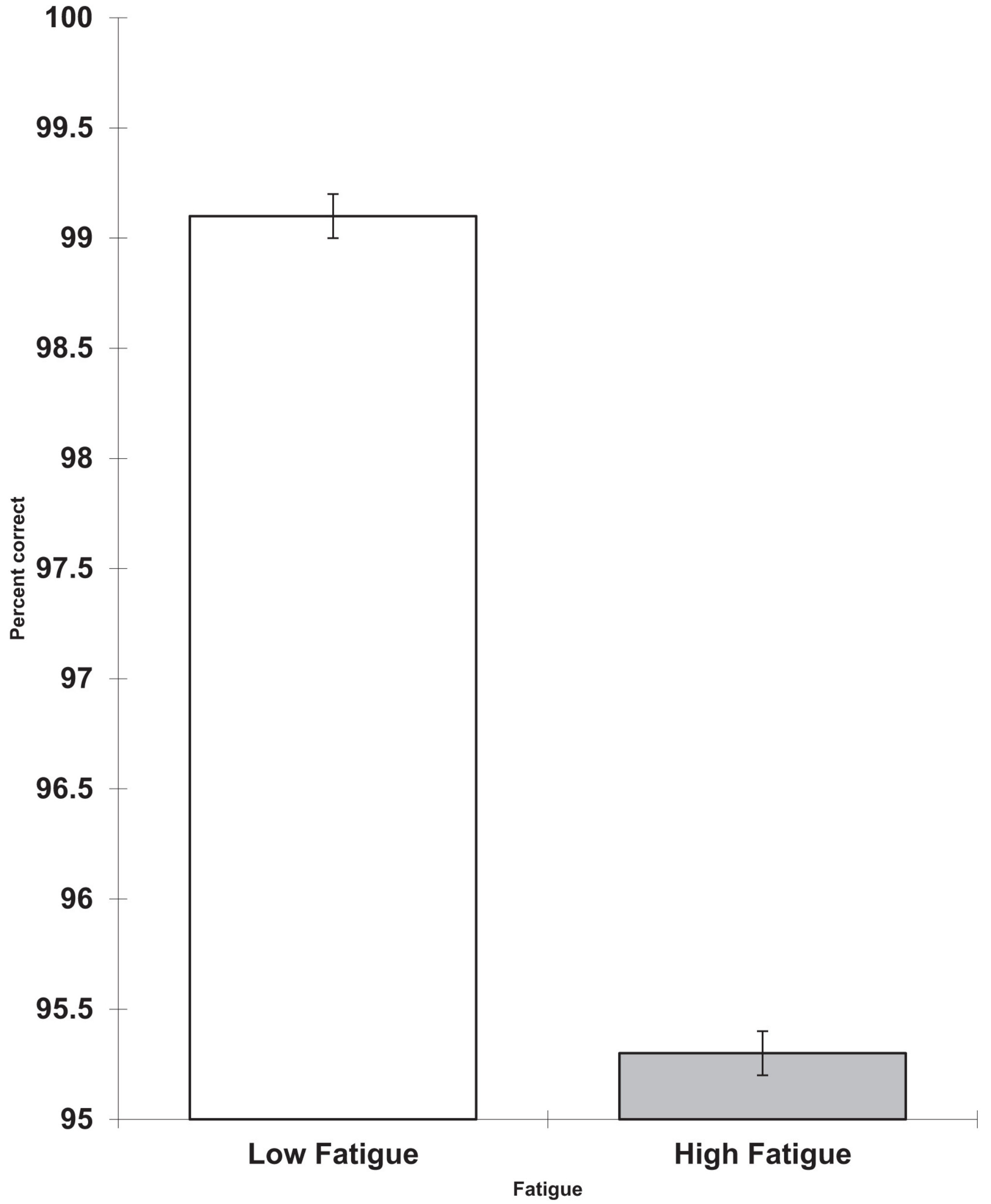

FIGURE 1 | Change in fatigue on Day 1 and visual search percent correct (scores are the adjusted means, standard errors (s.e.s) shown as bars.

extra instruments of objective measurement was not allowed, as this might create distractions and pose other potential safety risks.

Overall, the results of this study with the staff sample were in line with those of previous studies, including our study with a student sample using the same performance tasks

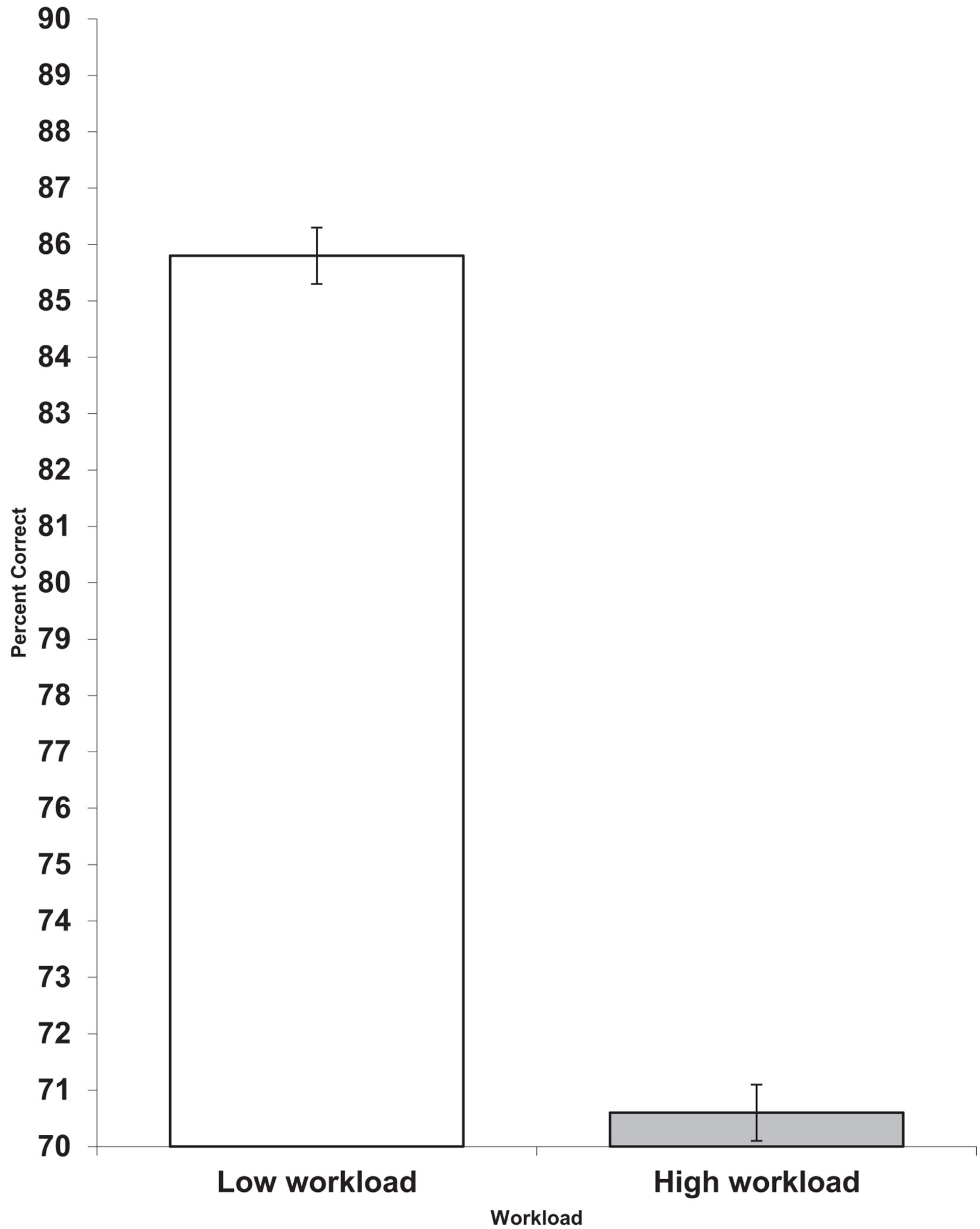

FIGURE 2 | Day 1 workload and logical reasoning percent correct (scores are the adjusted means, s.e.s shown as bars).

(Fan and Smith, 2017) and those carried out in different transport industries (Feyer and Williamson, 2001; Smith et al., 2006; Smith and Smith, 2017) which found that performance was impaired by fatigue. The effects of fatigue on cognitive performance were found with both high and low workloads. However, there was some evidence of independent effects of workload on performance speed, although such effects were less frequent than those of fatigue. In addition, subjective fatigue increased, and general outcomes got worse at the end of the week, suggesting an effect of cumulative work fatigue on outcomes throughout the working week. This result was very similar to fatigue observed in seafarers, which increased day by day during the tour of duty and continued into leave (Bal et al., 2015).

The main hypothesis of the current study predicted that increased occupational fatigue would lead to performance reduction, including slower RT and lower accuracy rates. Comparable to our student sample study (Fan and Smith, 2017), the results here showed that an increased feeling of fatigue was associated with impaired performance, including decreased accuracy in the visual search task and slower RT in the logical

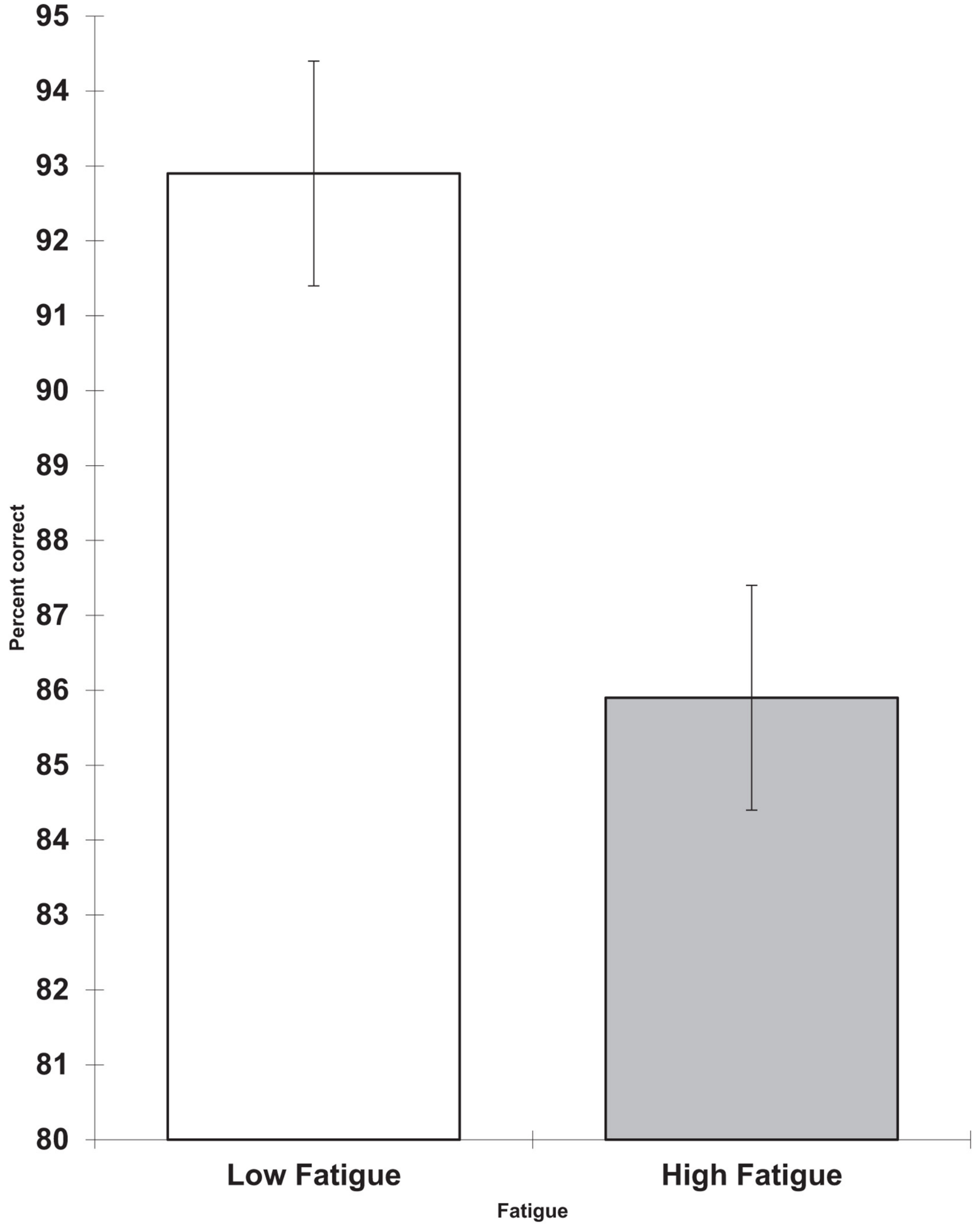

FIGURE 3 | Day 4 fatigue and visual search percent correct (scores are the adjusted means, s.e.s shown as bars).

reasoning task, which supports this hypothesis. The effects of workload were restricted to less accurate performance of the logical reasoning task on the first day.

This study was performed in the United Kingdom and the results were obtained using a United Kingdom sample, and differences in culture (Barlas and Obhi, 2014) were not relevant here. Previous studies have shown that fatigue impaired cognitive performance (e.g., Craig and Cooper, 1992; Beurskens et al., 2000), which was supported by the current study. The results from previous studies also suggest that it could be the increased fatigue, decreased control, and increased automation in the working environment which resulted in the changed sense of agency (e.g., Berberian et al., 2012; Kumar and Srinivasan, 2012, 2013; Moore, 2016; Howard et al., 2016; Di Plinio et al., 2019, 2020). The modern railway industry has increased the level of automation in operating systems and decreased control by operators (Young et al., 2015; Fan and Smith, 2019), and future studies of fatigue in railway staff samples should focus on changes in the sense of agency.

This study investigated the effect of occupational fatigue on cognitive performance in railway staff, and its results provide insight on current practices regarding fatigue management in

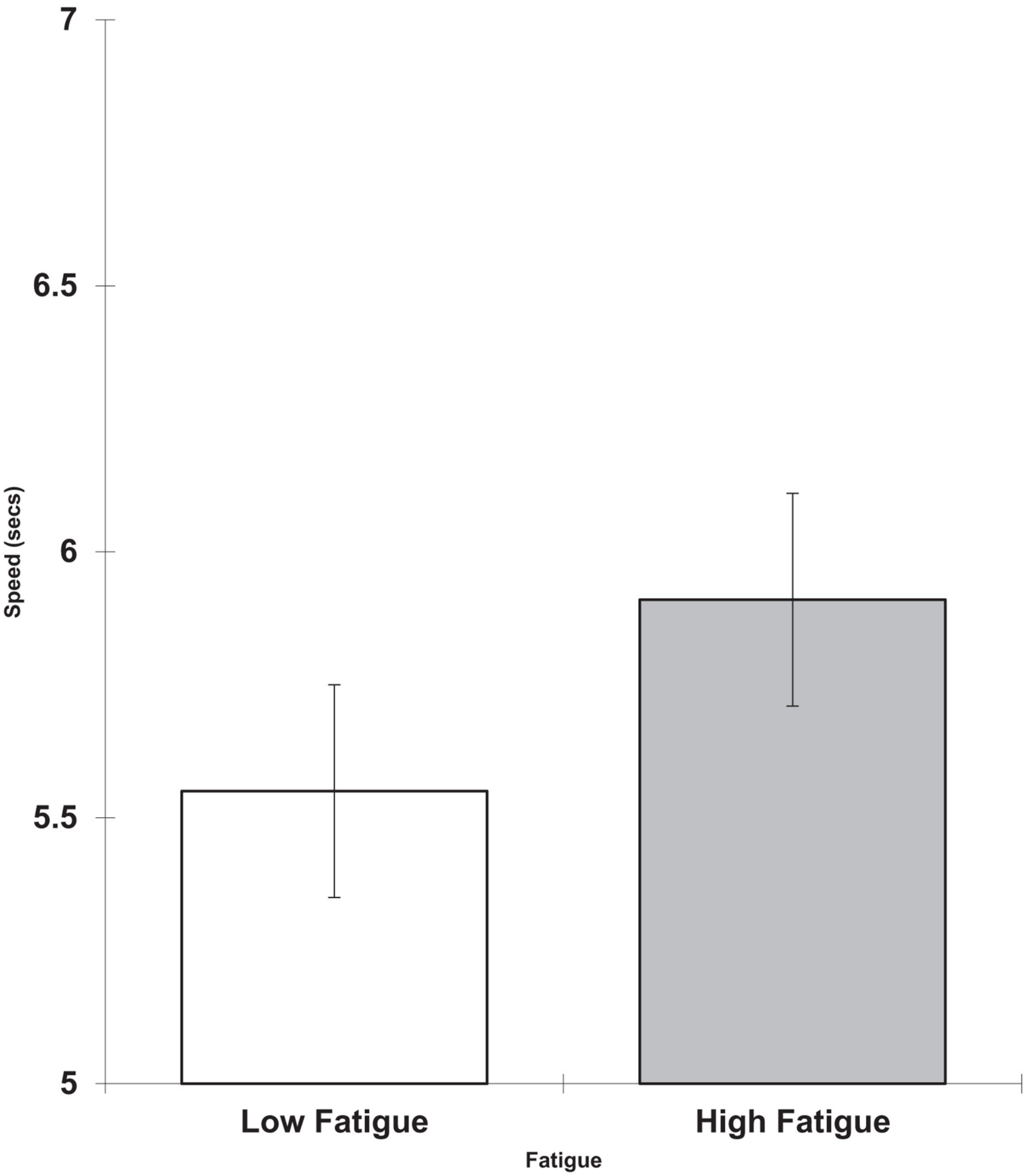

FIGURE 4 | Day 4 fatigue and logical reasoning speed (seconds per item; scores are the adjusted means, s.e.s shown as bars).

the industry. The findings allow us to offer a few suggestions for the railway industry. In general, either organizations or individuals should raise the issue of fatigue and its after-effects, and take action to prevent and manage it and related impaired performance in the workplace. The present research, in line with previous studies (e.g., Dorrian et al., 2011; Fan and Smith, 2017), indicated that workload should be considered as well as fatigue. Considering the nature of jobs in the railway industry, however, it will be not easy to control or reduce the workload, especially with the unpredictability of train problems and unplanned overtime work. Thus, companies and organizations can apply such online fatigue self-assessment and cognitive performance tasks to assess staff fatigue level before and after work. For those with no indication of fatigue, this will not change the normal working behavior of during their duty. For those with fatigue this can be prevented and managed by providing support (e.g., fatigue managing advices or intervention) during times when fatigue is likely to be at a high-risk level. Also, companies may need to improve work patterns and arrange rest times during and after work for recovery from fatigue, which reduces the risk of future fatigue-related performance impairment.

Limitations

The first sets of limitations are common in diary studies. As a method, the online diary study is less controlled than laboratory experiments, although it has the advantage of assessing the effects of fatigue in the context of participants' daily work lives, as well as being able to assess the effect of cumulative fatigue for a longer period of time than in laboratory experiments. One issue is completion of the diary at the correct time. One participant commented that he did not have time to complete the diary immediately after work because he was off very late and caught transport to return home in a hurry. Although this participant completed the post-work diary immediately upon arriving home, his fatigue and performance may have recovered during the commute. Another problem is the completion of the study. Diary studies are also time-consuming, and participants required reminders and encouragement to fully complete the diaries. In this study, it was difficult to recruit participants and have them fully complete all of the four sessions, especially the post-work diary on the last day of the work week. The majority of participants who forgot to fill in the last diary decided to quit the study rather than re-do it. This meant that the major limitation of the present study was the small sample size. The small sample size also meant that it was not possible to consider individual differences, such as job type or the personality of the participants.

Future Research

The current study was an initial trial of studying the effect of fatigue on performance in a real-life setting. There is a plan to conduct more staff experiments to further investigate the effects of fatigue on performance, as well as intervention experiments. Future research requires better control of online diary data collection. While the online diary is an advanced method for assessing fatigue closely in the context of daily work life, reminder texts or e-mails are needed to ensure that participants fill out each diary on time. The diary could be integrated with the HSE Fatigue and Risk Index (a fatigue prediction tool based on shift patterns currently used in the United Kingdom rail industry) in a future study. Although the job demands variable in this index is usually set at a constant level for all staff, it can be measured through the single-item self-assessment in the diary.

CONCLUSION

Occupational fatigue is an important issue in the rail industry and it can endanger passenger, staff and train safety. It is also important in jobs which are not safety critical as it can influence the efficiency of the organization and the health and wellbeing of staff. Our previous research has examined this issue in drivers (Evans, 2019), conductors, guards, and engineers (Smith and Smith, 2017). There is now a need to demonstrate the relationship between workload, fatigue, and performance among a wider range of staff of train operating companies. The present study was carried out in the workplace using an online methodology with both subjective and objective measurements. The aim was to examine the relationship between workload, fatigue, and cognitive performance using staff from a train operating company. The "After-Effect" technique was used with online diaries and cognitive performance tasks assessing the fatigue, work experiences, and performance of staff before and after work on the first and fourth days of one working week.

This field study provided evidence for the relationship between work-related fatigue and performance impairment. The findings show the need for future work on predicting fatigue-related performance decrements, and the necessity of providing interventions and support so that the risk to safety can be reduced. The results demonstrated that the objective performance of staff was impaired due to fatigue, shown as decreased accuracy on a visual search task and the logical reasoning task. These findings were in line with those of previous research in other work contexts. Increased fatigue was associated with higher workload, while fatigue before work was also associated with the quality and duration of sleep. Considering it is not easy to control or reduce the workload due to the nature of the jobs, the rail industry could focus instead on improving the guidelines regarding rest to manage fatigue, which would then reduce the risk of work performance impairment. Future research using an online diary should consider recruiting a larger sample and mitigating the risk of absent or incomplete diary entries.

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 School of Psychology Research Ethics Committee at Cardiff University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AS formulated the research question, designed the study, and revised the manuscript for important intellectual content. JF conducted the analyses, interpreted the data, and drafted the original manuscript. Both the authors approved the final version for publication and also agreed to be held accountable for all aspects of the work in ensuring that questions related to accuracy and integrity are appropriately investigated and resolved.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.558520/full#supplementary-material

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SYSTEMATIC REVIEW
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The Effect of Mindfulness-Based Intervention on Brain-Derived Neurotrophic Factor (BDNF): A Systematic Review and Meta-Analysis of Controlled Trials

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Background: This systematic review aims to answer three questions. First, how much do mindfulness-based interventions (MBIs) affect peripheral brain-derived neurotrophic factor (BDNF)? Second, do mindfulness exercise–based interventions (exercise-MBIs) and mindfulness meditation–based interventions (meditation-MBIs) affect peripheral BDNF differently? Third, does the age of participants and the accumulative hours of MBI practice affect peripheral BDNF?

Methods: We included randomized controlled trials comparing MBI and no intervention in adults (age >18 years) who reported peripheral BDNF. Database searches included PubMed, CINAHL, CENTRAL, PsyInfo, and Scopus. Two reviewers independently selected the studies and assessed the trial quality. We used the standardized mean difference (SMD) as the effect size index and conducted moderator analyses.

Results: Eleven studies are included in this systematic review. Five studies applying exercise-MBI and three studies applying meditation-MBI are included in the meta-analysis ($N = 479$). The pooled effect size shows a significantly greater increase of peripheral BDNF in MBI groups compared to the control groups ($k = 8$, $N = 479$, SMD $= 0.72$, 95% CI 0.31–1.14, $I^2 = 78\%$). Significantly more increases of BDNF in the MBI groups are found in both subgroups of exercise-MBI and meditation-MBI. The effect sizes of both subgroups are not significantly different between subgroups ($\chi^2 = 0.02$, $p = 0.88$). We find no significant correlation between the effect sizes and the age of participants ($r = -0.0095$, $p = 0.45$) or accumulative hours of MBI practice ($r = 0.0021$, $p = 0.57$).

Conclusion: The heterogeneous data of this small sample-size meta-analysis suggests that MBI can increase peripheral BDNF. Either exercise-MBI or meditation-MBI can increase peripheral BDNF.

Keywords: brain-derived neurotrophic factor, BDNF, mindfulness, meditation, neuroplasticity

INTRODUCTION

It is well-established that brain-derived neurotrophic factor (BDNF), a neuronal growth factor, affects neuronal survival and regeneration, called "neuronal plasticity" (Lu et al., 2014). Hence, there is increasing interest in the potential therapeutic effect of interventions that increase BDNF (Bathina and Das, 2015). BDNF is produced in both the central nervous system and peripheral tissues. The BDNF measured from blood, either from serum, plasma, or saliva, is called peripheral BDNF. Previous studies show peripheral BDNF is related to numerous brain disorders. A recent meta-analysis finds that lower levels of peripheral BDNF are associated with an increased risk of depression (Brunoni et al., 2008), Alzheimer's disease (Balietti et al., 2018), Parkinson's disease (Rahmani et al., 2019), and strokes with an unfavorable outcome (Xu et al., 2018). There have been attempts to provide external BDNF, but this has not been successful (Houlton et al., 2019) due to poor blood–brain barrier permeability and short therapeutic half-life (Poduslo and Curran, 1996). Some studies claim that acetylcholinesterase inhibitors and antidepressants may increase peripheral BDNF (Ströhle et al., 2015); however, the evidence still needs to be evaluated (Zhou et al., 2017). Currently, it would be safer and more feasible to promote lifestyle modification that increases BDNF.

Mindfulness, in a focused-attention practice, has been developed to be a health intervention. Mindfulness has been defined as "paying attention in a particular way, on purpose, in the present moment, and non-judgmentally" (Kabat-Zinn, 2003). Mindfulness-based interventions (MBIs) are practices that employ a variety of techniques designed to facilitate mindfulness to affect bodily function and symptoms. Regarding this definition, MBI can be divided into (1) mindfulness-based exercise, which emphasizes body movement, such as yoga, tai chi, and qi gong, and (2) meditation and its derivatives, which emphasize mentality training, such as mindfulness breathing, compassionate body scan, and working with emotions through imagination. This latter type of MBI also includes secular therapy like mindfulness-based stress relaxation (MBSR) and mindfulness-based cognitive therapy (MBCT) (Goldberg et al., 2018).

Numerous studies show that practicing MBI affects brain structure and function. In a meta-analysis of 21 studies, Fox and colleagues applied diffuse tensor imaging and voxel-based morphology imaging MRI to 300 meditation-naïve participants. They find brain changes, namely a moderate increase in brain size, in eight regions. These brain regions are the hippocampus, anterior and midcingulate gyrus, frontopolar cortex, sensory cortices and insula, orbitofrontal cortex, superior longitudinal fasciculus, and corpus callosum (Fox et al., 2014). Another meta-analysis of 18 studies of MBSR and MBCT also finds the improvement of working memory, autobiography memory, and cognitive flexibility after practicing MBI (Lao et al., 2016).

Similar to other interventions affecting brain function, MBIs have been assessed regarding their effects on the brain using the measure of peripheral BDNF. A recent meta-analysis finds that physical exercise, including mindfulness-based exercise (e.g., yoga, tai chi) increased peripheral BDNF (Dinoff et al., 2016). Because mindfulness-based exercise comprises light-to-moderate exercise and mindfulness meditation, it is not yet known if mindfulness meditation plays any role in such an increment (Ainsworth et al., 2000). Another study examining the effect of yoga on peripheral BDNF also reports that the increased peripheral BDNF is negatively correlated with age ($r = -0.446$) (Pal et al., 2014). In addition, a meta-analysis reports that cumulative hours of physical exercise is an effect modifier of peripheral BNDF increment (Dinoff et al., 2017).

The evidence mentioned above suggests that the effect of MBIs, especially the meditation part, on peripheral BDNF remains inconclusive. This systematic review and meta-analysis aims to answer three questions. First, how much does MBI affect peripheral BDNF? Second, do mindfulness exercise-based interventions (exercise-MBIs) and mindfulness meditation-based interventions (meditation-MBIs) affect peripheral BDNF differently? Third, does the age of MBI practitioners and the accumulative hours of MBI practice affect peripheral BDNF?

MATERIALS AND METHODS

The protocol of this systematic review (CRD42018093786) is registered at PROSPERO (International Prospective Register of Systematic Reviews). This present report follows the format of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) Statement.

Inclusion Criteria of Studies

Studies that are included meet the following criteria: (i) a parallel or crossover randomized, controlled trial (RCT) in adults (age > 18 years); (ii) the experimental group receiving any type of MBI; (iii) the comparator group receiving no treatment, treatment as usual, or being on the waitlist; and (iv) the changes in plasma or serum BDNF after receiving MBI being reported or calculable.

Our meta-analysis does not include non-controlled (single-arm) trials due to the presence of confounding factors. One of the important confounders is called the "vacation effect." This effect is reported in some studies that show the non-intervention group also had peripheral BDNF changes during follow-up (Epel et al., 2016; Kwak et al., 2019). The BDNF changes suggesting a vacation effect, refers to the temporary improvements in health and psychological well-being after taking a vacation, which soon fade after work resumption (Goldberg et al., 2018). However, improved reliability should result from the balance of confounders in the comparison groups of RCTs. For this reason, it was decided to include only RCTs in our meta-analysis.

Data Sources and Searches

Searches were conducted on PubMed, EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL), and CINAHL (nursing and allied health professions), and PsyInfo from inception (2008) up to June 2020. For all full-text articles that passed the screening, their reference lists were examined to identify additional relevant studies ("snowball" method).

Study Selection and Quality Assessment

Two reviewers (PG and NY) independently selected the searched records, extracted the data, selected the studies, and assessed the trial quality. If any discrepancy existed, other investigators would additionally review and discuss with the first two reviewers to form a consensus.

After the completion of study selection, the data was extracted as recommended by the Center for Reviews and Dissemination. Each trial was evaluated using the Cochrane Collaboration four criteria for assessing the risk of bias. Those include (i) adequate generation of allocation sequence, (ii) concealment of allocation, (iii) prevention of knowledge of the allocated intervention, (iv) dealing with an incomplete data set, (v) selective report, and (vi) other bias.

Data Extraction

Apart from demographic and clinical characteristics, the changes in peripheral BNDF are the outcome of interest. In comparison to the endpoint peripheral BDNF, the mean changes are preferred because the included studies are likely to have small sample sizes. We declined to use the endpoints of peripheral BDNF because baseline data of paired groups enrolled in a small study might not be comparable although the randomization was applied.

The mean changes and standard deviations (SDs) of peripheral BDNF were extracted. If the study in which the means and SDs of BDNF level changes were not available, the means and SDs at baseline and endpoints were used to calculate the means and SDs of BDNF level changes. To estimate the SD of mean change of BDNF level changes, the baseline and postintervention correlation coefficient (r) were needed. If such r was not available, r was defined as 0.5 for the treatment group and 0.05 for the control group. This estimation was obtained from Ledreux et al. (2019), which is the only study that clearly reports the Pearson r for mindfulness practice $= 0.439$ and Pearson $r = 0.037$ for the control group.

Meta-Analysis

Because peripheral BDNF can be measured by various laboratory kits and reported in many unit systems, the standardized mean difference (SMD) is used as the effect size index. The present SMD is defined as the difference between the mean change of peripheral BDNF obtained from the experimental group and that obtained from the control groups. This, in turn, is divided by the pooled within-group SD. This is an appropriate index when the subjects are randomly assigned to the comparison groups with the assumption that both groups are equivalent at baseline (Rubio-Aparicio et al., 2018).

Heterogeneity is estimated using the I^2 statistic. If the heterogeneity of data is significantly high ($I^2 > 50\%$), effect sizes are pooled using a random-effect model. The effect sizes are interpreted as Cohen's recommendations: 0–0.19 = negligible effect, 0.20–0.49 = small effect, 0.50–0.79 = moderate effect, 0.80 or more = large effect (Schäfer and Schwarz, 2019). The publication bias is assessed visually using the funnel plot as in **Figure 1**. The number of trials expected to be able to be included in the meta-analysis is <10. Begg's test for funnel plot symmetrical also applies (Begg and Mazumdar, 1994).

Moderator Analyses

A subgroup analysis was conducted by separating the included studies into three subgroups based on the types of MBI. These included (i) exercise-MBI (e.g., yoga, tai chi), (ii) meditation-MBI, and (iii) other MBI practices (e.g., MBI added on other programs). Two meta-regression analyses were performed by computing the correlation coefficients (rs) between (i) the effect sizes and the average ages of participants and (ii) the effect sizes and the accumulated hours of MBI practice. The accumulated hours of MBI practice of each study were computed by multiplying the practice hours per week with the number of study weeks.

Software

All analyses and most of Figures were conducted using R 4.0 (R Core Team, 2016) and Figure 2 was produced by Robvis (McGuinness and Higgins, 2020).

RESULTS

Study Characteristics and Quality

The searches retrieved 522 records in total (see **Figure 1**). After the removal of duplicated records, record screening, and assessment of full-text articles, 11 studies met the inclusion criteria and are included in this systematic review. All studies were conducted in adults with a median age of 48 (range 31–84) years, slightly predominantly female with common diagnoses of psychiatric problems and low burdens of physical health. The median accumulative intervention exposure was 28 h (range 8–158 h). **Table 1** shows other characteristics of the included studies. The included studies pose a low-to-moderate risk of bias. The common risk is that no study could blind interventions. **Figure 2** shows other issues of methodological quality in the included studies.

Of 11 included studies, five (Ikai et al., 2014; Naveen et al., 2016, Tolahunase et al., 2017; Sungkarat et al., 2018) and three (Fox et al., 2014; Gagrani et al., 2018; Nery et al., 2019) studies are parallel RCTs applying exercise-MBI and meditation-MBI, respectively. These eight studies had a follow-up duration between 8 and 36 weeks. Due to their similarities, these eight studies are included in the meta-analysis ($N = 479$).

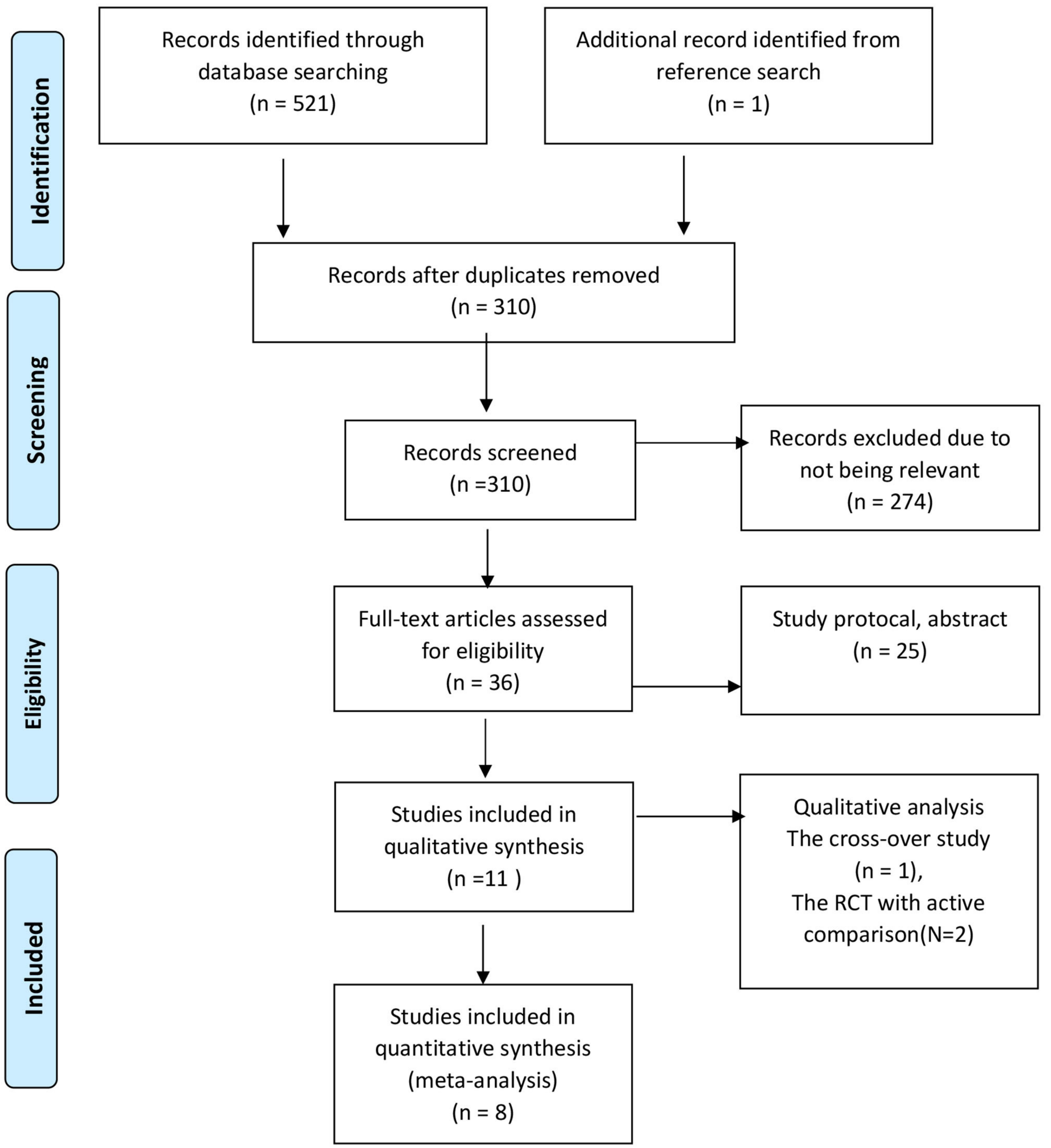

FIGURE 1 | Algorithm of study selection following PRISMA guideline.

The three following studies (Håkansson et al., 2016; Montero-Marin et al., 2019; Ng et al., 2020) are very dissimilar in character of intervention and control group to the first eight studies. They are included in the qualitative analysis only. Håkansson et al. conducts a crossover study in 19 healthy elders. However, this study was excluded because it applied only active interventions of cognitive training and physical exercise in the control arms. All participants went through different training commercial applications for 35 min each. The study measured the peripheral BDNF within 0, 20, and

TABLE 1 | The included studies for systematic review (*Not included studies in the meta-analysis).

Study	Study design	Participant condition and number	Average age of participants	Intervention	Control	Accumulative hours of mindfulness intervention practice	BDNF baseline and post-intervention	BDNF change from baseline comparing intervention and control (effect size, SE)
MINDFULNESS BASED EXERCISE								
Lee et al. (2014)	Parallel RCT	low back pain with depression $N = 25$	40.5 F 100%	Yoga	Regular lifestyle	1 h X 3 times/week X 12 weeks = 36 h	Serum, ng/ml baseline 23.97 post 30.39	1.52 (0.46) Intervention increase more than control
Ikai et al. (2014)	Parallel RCT	Schizophrenia $N = 50$	52.8 F 35%	Yoga + standard treatment	Standard treatment	1 h X 1 times/week × 8 weeks = 8 h	Plasma ng/ml baseline 0.149 post 0.190	−0.06 (0.28) intervention increase less than control
Naveen et al. (2016)	Parallel RCT	Depression $N = 44$	33.5 F 45%	Yoga + standard treatment	standard treatment	1 h X 1 times/week × 12 weeks =12 h	Plasma ng/ml baseline 0.203 post 0.214	0.74 (0.34) Intervention increase more than control
Tolahunase et al. (2018)	Parallel RCT	Depression $N = 58$	39.4 F 15%	Yoga + standard treatment	Standard treatment	120 min × 12 weeks = 168 h	Serum, ng/ml baseline 13.5 post 18.6	1.01 (0.28) Intervention increase more than control
Sungkarat et al. (2018)	Parallel RCT	Mild cognitive impairment $N = 66$	67.5 F 80%	Tai Chi	Regular lifestyle	50 min × 3 times/week × 24 weeks = 60 h	Plasma, ng/ml baseline 0.1123 post 0.385	0.12 (0.24) Intervention increase more than control
MINDFULNESS MEDITATION AND DERIVATIVES								
Gagrani et al. (2018)	Parallel RCT	primary angle glaucoma $N = 60$	57.28 F 42%	Meditation	Regular lifestyle	45 min × 7 times/week × 6 weeks = 31.5 h	Serum, ng/ml baseline 52.24 Post 63.25	0.13 (0.25) Intervention increase more than control
Ledreux et al. (Ledreux et al., 2019)	Parallel RCT	Healthy N =78	72.9 F=70%	Meditation	Regular lifestyle	3 h per weeks × 5 week = 15 h	Serum, ng/ml baseline 26.60 post 26.59	1.18 (0.69–1.16) Intervention decrease less than control
Nery et al. (2019)	Parallel RCT	Infertility with anxiety N =62	37.2 F 100%	Meditation	Regular lifestyle	2 h per week for 8 weeks = 16 h	Serum, ng/ml baseline 84.64 post 91.92	0.58 (0.21) Intervention increase more than control
(Håkansson et al., 2016)*	Crossover trial control trial	Healthy $N = 57$	70.2 F 58%	Mindfulness practice	Physical exercise, Cognitive training	35 min	Serum, ng/ml Pre-crossing 21.6 Post 21.05	−0.55 (1.27) Mindfulness and cognitive training did not change while physical exercise increase
(Montero-Marin et al., 2019)*	Parallel RCT	Fibromyalgia $N = 24$	53.05 F 100%	Attachment-based compassion therapy (ABCT)	Relaxation technique	2 h per week × 8 weeks + 2 h per month × 3 months = 32 h	Serum, ng/ml, baseline 23.03 post 16.03	−1.56 (0.4) Intervention decrease more than control
Siang Ng et al. (2020)*	Parallel RCT	Mild cognitive impairment $N = 55$	71.28 F 70%	Mindfulness Awareness Practice (MAP)	Health education Program	1 h per week × 12 weeks + 1 h per month x 6 months =18 h	Serum, log transformation adjusted mean baseline 7.238 post 6.323	−1.61 (0.31) BDNF decrease in both intervention and control group.

**Not include in met analysis.*

60 min after finishing each intervention. They find peripheral BDNF in those receiving physical exercise is significantly increased from a baseline although mindfulness and cognitive training show no significant change. There were two studies related to disease-specific mindfulness programs compared to active interventions. Montero-Martin et al. conducted a parallel RCT in patients with fibromyalgia. They compare attachment-based compassion therapy (ABCT), a fibromyalgia-specific mindfulness-based program with relaxation therapy. The study shows the ABCT group had a significantly greater improved quality of life concurrent with a greater reduction of BDNF. Siang Ng et al. conducted a parallel RCT in elders with mild cognitive impairment. The intervention was a modified MBSR program for the cognitively impaired person called mindful-awareness practice (MAP). The control arm received a lifestyle modification health education program. The study resulted in BDNF in both MAP and control groups reduced from baseline at 3 and 9 months of the program.

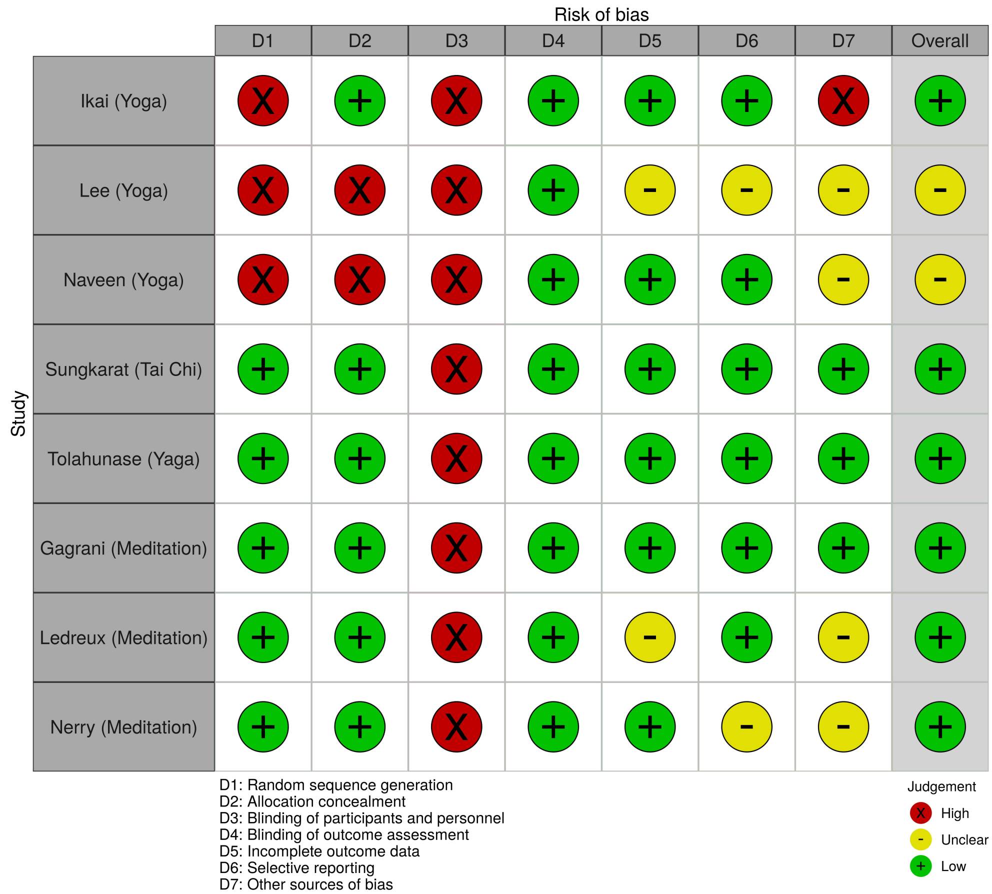

FIGURE 2 | The quality of research.

Meta-Analysis

Figure 3 shows the meta-analysis of the eight included studies using a random effect model. The pooled effect size shows a significantly greater increase of peripheral BDNF in MBI groups compared to the control groups (k = 8, N = 479, SMD = 0.72, 95% CI 0.31–1.14, I^2 =78%). Regarding the publication bias, the funnel plot of effect sizes against their standard errors shows a relative symmetry of plots. The Begg's rank test of funnel plot asymmetry indicates no significant asymmetry of effect-size plots (k = 8, z = 0.72, p = 0.45) in **Figure 4**.

Moderator Analyses

Figure 3 shows the subgroup analysis comparing the pooled effect sizes of BDNF changes between the exercise-MBI and control groups and between the meditation-MBI and control groups. In the MBI groups, significantly greater increases in peripheral BDNF are found in both subgroups (k = 5, N = 242, SMD = 070, 95% CI = 0.12–1.29, I^2 = 78%) and meditation-MBI (k = 3, N = 237, SMD = 077, 95% CI = 0.07–1.48, I^2 = 85%). The effect sizes of both subgroups are not significantly different between subgroups (χ^2 = 0.02, p = 0.88).

The meta-regression analyses shows no significant correlation between the effect sizes and participants' age (r = −0.0095, p = 0.45) or accumulative hours of practice (r = 0.0021, p = 0.57) (see the bubble plot in **Figure 5**).

DISCUSSION

Our meta-analysis examines the effect of MBI on peripheral BDNF by including eight RCTs (N = 479). Based on the heterogeneous data, it is found that MBIs can increase peripheral BDNF. The increases in peripheral BDNF are not different between those practicing exercise-MBI and meditation-MBI.

The practitioners' age or the accumulative hours of MBI practice do not appear to be effect modifiers on peripheral BDNF affected by MBIs.

The present evidence supports previous findings and extends our knowledge in this area. The present meta-analytic results are in line with the report that mild-to-moderate exercise incorporated in MBI (e.g., yoga, tai chi) can increase peripheral BDNF. However, our subgroup analytic results extend current knowledge that not only exercise-MBI but also meditation-MBI can increase BDNF. This new knowledge suggests that, for exercise-MBI, both components of exercise and meditation contribute to the increase of peripheral BDNF.

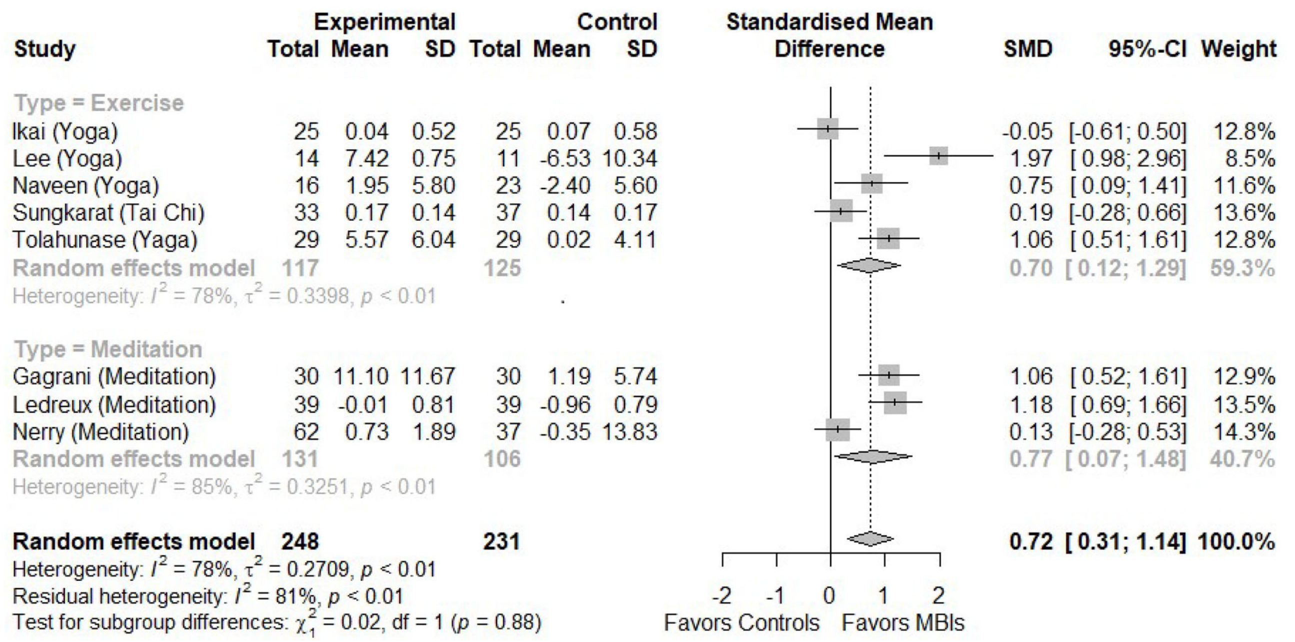

FIGURE 3 | The forest plot of included studies (K = 8).

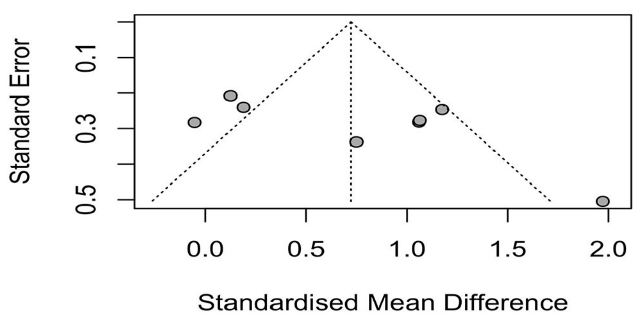

FIGURE 4 | The funnel plot. K = 8, The Egger's test for publication bias: t = 1.7856, df = 6, p = 0.1244.

Our meta-regression analytic results suggest that effect modifiers of peripheral BDNF changes affected by physical exercise may not be applicable for MBI. Previous studies report that practitioners' age and hours of practice are associated with the changes in peripheral BDNF related to yoga or exercise practice (Dinoff et al., 2016; Lao et al., 2016). However, our meta-analyses does not show the association of those effect modifiers in MBI practitioners. It is possible that the inclusion of three meditation studies, which are non-exercise-based interventions, may reduce the strength of such association. In addition, the small sample sizes of the included studies might cause a type II error, which results in the discovery of false-negative findings.

Håkansson et al. (2016) shows that a short bout of mindfulness does not change peripheral BDNF. He hypothesizes that physical exercise and mindfulness meditation may increase blood BDNF via a different mechanism. This may imply the relatively delayed effect of mindfulness on peripheral BDNF. One possibility is that blood BDNF increases from BDNF efflux from the brain. However, this hypothesis has a counter-argument; because BDNF has a relatively short half-life (around 45 min), it may disappear before getting through the blood–brain barrier (Poduslo and Curran, 1996; Pan et al., 1998). Another possible explanation is that mindfulness can reduce systemic inflammation and free radicals, which help reduce BDNF eradication (Yang et al., 2017). This is supported by a previous meta-analysis, in which MBI, both exercise-MBI and meditation-MBI, show a significant correlation with clinical improvement. Concurrently, there is also a significant correlation with reduced inflammatory biomarkers, specifically salivary levels of interleukin 6 and tumor necrosis factor-alpha in depression and generalized anxiety disorder (Hofmann et al., 2010; Sanada et al., 2020).

There might be a unique interaction between MBI and chronic pain. A study in patients with fibromyalgia (Montero-Marin et al., 2019) shows participants had decreased BDNF concurrent with improving pain symptoms after the intervention and active intervention control. The author refers to a result supported by clinical observations that, in patients with central sensitivity pain syndrome, during the active symptoms, peripheral BDNF is higher than when symptoms are improving (Deitos et al., 2015). Preclinical studies find that BDNF might be involved in maladaptive mechanisms in neuropathic pain, spasticity, and convulsive activity (Smith, 2014). Hence, more studies on the effect of MBI on BDNF in chronic pain syndrome are warranted.

The low adherence to mindfulness practice can mask the effectiveness of MBI for BDNF. Ng et al. report decreased BDNF in both intervention and control groups after 9-months follow-up. The author discusses that low compliance to homework mindfulness practice in mild cognitive impairment might influence the result. This is supported by a meta-analysis that finds adherence to home practice significantly impacts the

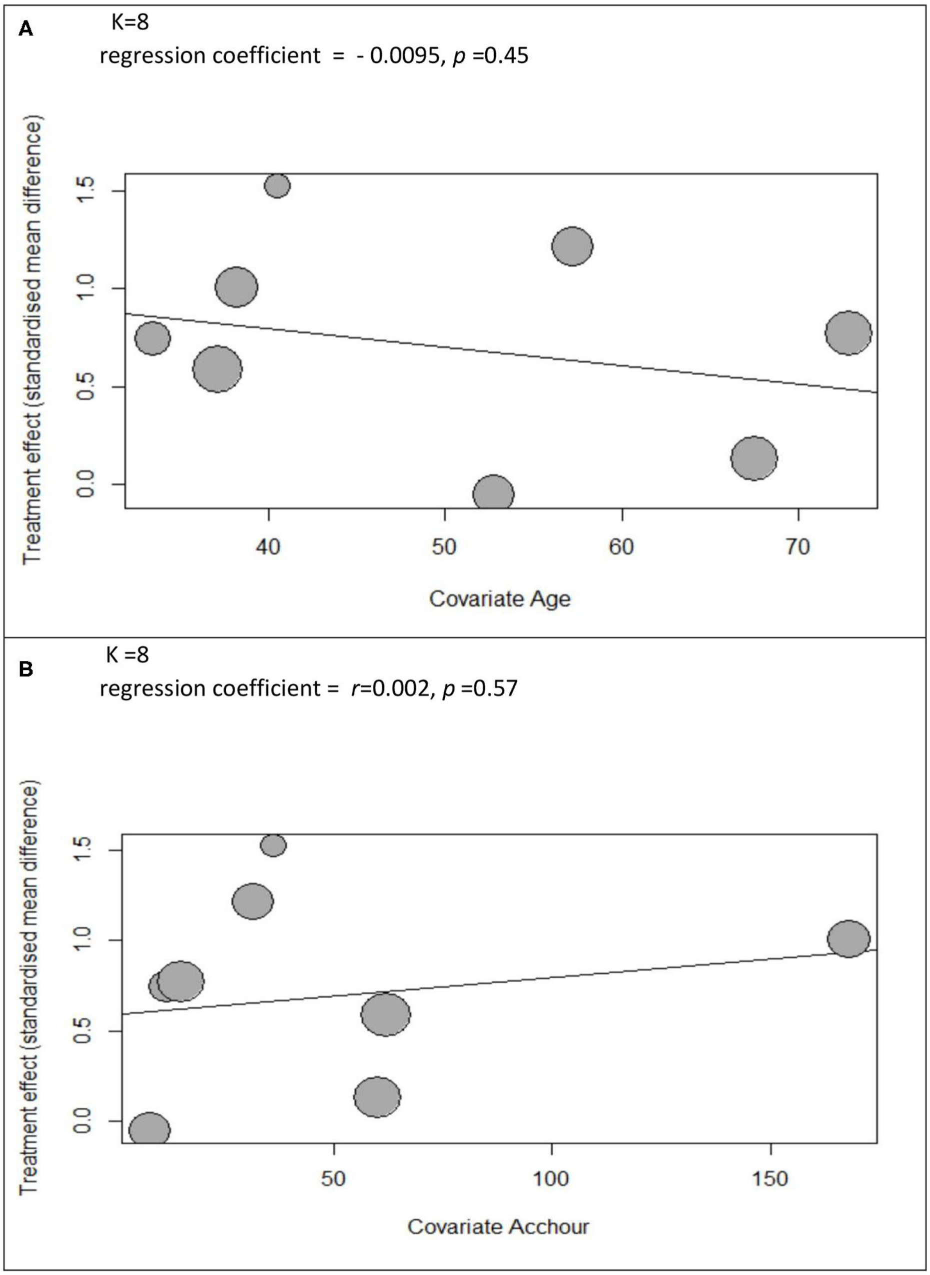

FIGURE 5 | The bubble plots of met regression analysis of **(A)** participants' age and **(B)** accumulated hours of practice.

effectiveness of MBI (Parsons et al., 2017). This lesson highlights the need to explore the optimum dose response for mindfulness practice to balance between achieving desired outcomes and being suitable for the participant's feasibility.

There are some limitations to this current systematic review. First, our review includes a smaller number of RCTs and participants compared to previous systematic reviews that include all trials examining the changes of peripheral BDNF affected by some interventions, e.g., physical exercise (Dinoff et al., 2016). This limitation may cause some type II errors in our statistical analyses, e.g., meta-regression analyses. As mentioned in the present method section, for the studies in this area, the data as well as the meta-analyses obtained from RCTs would be more reliable. However, second, the majority of participants in our meta-analysis are mentally ill and have a low burden of physical health problems. The generalizability of the present results to other groups of patients may be limited. Third, there is a lack of detailed information about factors that may affect peripheral BDNF across each study discussed before; such as the intervals between the last session of intervention and blood obtainment, the proportion of participants with chronic pain syndrome, and adherence to the mindfulness program. Last, the exclusion of non-English articles might raise the risk of publication bias.

More studies in this area remain needed. These include head-to-head RCTs comparing the effects of exercise-MBI and meditation-MBI on peripheral BDNF. Because BDNF activities are also related to physical illnesses, studies of metabolic syndrome as well as patients with chronic pain syndrome should be also carried out.

Despite the above limitations, the present findings are still helpful for clinical practice, in particular, the patients with a physical disability. Increased BNDF may decrease emotional problems. Meanwhile, more exploration is needed on the influence of chronic pain syndrome and the aging brain on the effect of MBI on BDNF. Many people may wish to increase their BDNF. For an individual without a physical disability, he/she can practice physical exercise to increase his/her BDNF. However, those who have a physical disability may choose to practice meditation-MBI to increase their BDNF.

CONCLUSIONS

The heterogeneous data of this small sample size meta-analysis suggest that MBI can increase peripheral BDNF. Either mindfulness exercise or mindfulness meditation-based intervention can increase peripheral BDNF. Patients with a physical disability may choose to practice MBI to increase their BDNF. More studies in this area are warranted.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study meets the criteria of Chiang Mai University for ethical approval and consent exemption (Exemption number 2561-05447).

AUTHOR CONTRIBUTIONS

PG and MS designed the study. PG and NY conducted the research. PG and MS conducted the meta-analysis. PG wrote the first draft of the manuscript. NC, SC, and MS participated in the revision of the subsequent draft. 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/fpsyg.2020.02209/full#supplementary-material

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PERSPECTIVE
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A Perspective on Implementing Movement Sonification to Influence Movement (and Eventually Cognitive) Creativity

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Creativity represents an important feature in a variety of daily-life and domain-specific contexts. Recent evidence indicates that physical movement serves as a key resource for exploring and generating task-relevant creative ideas, supporting the embodied perspective on creative cognition. An intuitive link between movement and creative cognition is movement creativity. The process of exploring the movement solutions an environment offers (i.e., affordances) and exploiting novel, functional, and creative movements may translate to and improve how individuals explore and generate novel ideas. Opening perception to the variety of affordances ("conventional" and novel) an environment offers drives creative movement. Teachers and coaches can promote this process by designing a learning environment that invites performers to consider and utilize novel movement solutions. In this article, we present a rationale for using movement sonification to promote creative movement. Movement sonification consists of mapping a movement parameter into sound, with a sound being triggered or changing according to how movement unfolds. We argue that movement sonification can facilitate the emergence of creative movement *via* enhancing perception of currently performed movements and invite performers to utilize novel affordances, and emphasizing information for regulating subsequent creative actions. We exemplify this concept in a creative dance intervention for children during physical education classes. In conclusion, we contend that learning to explore original dance sequences using movement sonification may provide a meaningful link between creative movement and creative cognition. Children may use their minds *and* bodies as tools for creative thinking and exploration, such as shaping letters with their bodies.

Keywords: creative cognition, embodied cognition, exercise-cognition, affordance, functional similarity, education, creative

INTRODUCTION

Creativity is a relatively new term with its genesis in the 20th century. In 1968, Wyrick was one of the first to explore an embodied approach to creativity research through emphasizing the importance of movement and its relationship with the environment (Wyrick, 1968). Creative cognition represents an important feature in a variety of daily-life and domain-specific contexts, and the embodied perspective on creative cognition contends that body movement plays a key and active role in the development of creative ideas. An intuitive link between body movement and creative cognition is creative movement. Creative movement is generally defined as a functional and original movement solution to achieve a task goal (Memmert and Perl, 2009; Hristovski et al., 2011), and could be instrumental for creative cognition given its prominence in the art and sport domains (e.g., dance). The process by which creative movement emerges may influence and enhance how creative ideas are generated. Importantly, broadening perception of what the task and environment offers and exploring different solutions to solve a motor task promotes creative movement and can eventually contribute to generating creative ideas. Here, we discuss how the strategy of sonifying a movement – movement sonification – can be used to promote creative movement. While this concept is not novel and sonification has been already used to promote creative movement, primarily in dance improvisation (e.g., Lem et al., 2010; Diniz et al., 2012; Rizzo et al., 2018; Dahlstedt and Dahlstedt, 2019; Erdem et al., 2019), we think that a clear rationale for its implementation in the context of movement creativity is lacking. We present our approach grounded in ecological psychology and discuss how movement sonification can invite performers to explore the variety of movement opportunities (i.e., affordances) the environment offers, thus promoting creativity. Importantly, we also highlight the potential implications that this approach and, more generally, creative movement can have on creative cognition.

CREATIVE COGNITION

Creative cognition is often understood as a collection of mental operations that promote the generation of novel and task- or context-relevant ideas (Sternberg and Lubart, 1999; Runco and Jaeger, 2012). Creative thinking is esteemed across many domains, including large-scale scientific achievement, technological innovation, and artistic expression (Cropley, 2006; Moran, 2010). However, small-scale creativity is also an important outlet for self-expression as individuals learn to initiate and pursue novel approaches to everyday problem-solving (Richards, 2010). Practicing everyday creative thinking may be particularly beneficial to the development of a cognitive skillset that lends itself to the fulfillment of creative thinking potential at more impactful levels. This is because, while ability, experience, and capacity indisputably influence the value of creative thoughts, the same cognitive processes are thought to contribute to the production of both seminal and everyday creative ideas (Runco, 2014).

Given the breadth and diversity of creative outcomes, our approach centers on highlighting the role of everyday creative thinking in context (Cropley, 2006; Amabile, 2018). Specifically, several foci of cognitive creativity research encompass strategies for increasing creative thinking in educational contexts (Craft, 2003; Beghetto and Kaufman, 2010; Moran, 2010; Pllana, 2019) by supporting holistic academic success, mental health and well-being, and reinforcing diversity and cross-cultural inclusivity (Lubart and Georgsdottir, 2004; Glaveanu et al., 2019). To this end, it is important to highlight that creative thinking is suggested to be less of an inflexible, enduring personality trait consigned to the minds of geniuses, and is considered more of an externally-modifiable faculty (Amabile, 2018). In other words, creative thinking is proposed to be shaped by both intrinsic factors, including task-relevant skills and motivation, as well as external circumstances, such as affordances and constraints within the task environment (Ward et al., 1999; Amabile, 2018). A context-centered perspective of creative cognition, therefore, permits a broader exploration of the value of everyday creative thinking as a conduit for the construction of meaning across the lifespan.

THE ROLE OF EMBODIMENT IN CREATIVE COGNITION

Understanding which mental and contextual factors may promote or inhibit creative thinking processes is integral to establishing models that adequately address creative cognition across domains (Ward et al., 1999). Embodied cognition frameworks interleave both mental and physical dynamics of problem-solving, contending that the mind, body, and environment shape the problem/task-goal space, and their interaction guides thought and action that are appropriate to solving the problem (Shapiro and Stolz, 2019). The body may support cognition by offering a means to manipulate and explore the problem-space and reduce cognitive load (Risko and Gilbert, 2016). For example, reading tilted words on a computer screen often requires physical movement (i.e., tilting the head) to accomplish this demanding task, rather than relying solely on mental rotation to match the tilted word stimuli with stored representations of normally-oriented text in semantic memory (Jolicoeur, 1988; Risko and Gilbert, 2016).

The role of movement for creative thinking may be particularly important from a developmental perspective, as a wealth of evidence suggests that early acquisition of motor skills is positively associated with cognitive developments, including memory, language, and problem-solving ability (see Frith et al., 2019). An important mechanism underlying the benefits of movement for cognition is functional similarity between task-relevant movement and cognitive process (Tversky, 2009). Functional similarity between mental and physical operations is thought to scaffold and offload cognition, meaning that the body is a conduit for meaningfully exploring and externalizing task-relevant solutions (both physical and mental). For example, Bara and Bonneton-Botté (2018) demonstrated that movement-based educational programs have the potential to support learning in early childhood compared to sedentary approaches.

In this study, kindergarteners were taught to (1) move their arms to draw letters in the air, and (2) walk along letter outlines drawn on the ground. This motor intervention was associated with higher letter recognition and handwriting quality compared to practicing visual recognition of letters and handwriting practice alone. Recent creativity work has also shown that moving *via* gesture (Kirk and Lewis, 2017), and matching (functionally similar) emotional states with physical exertion in dance (Hutton and Sundar, 2010) promoted divergent thinking performance. These findings offer additional credence to the purported role of functional similarity within the mind-body relationship. Taken together, physical movement may serve as a resource for exploring and generating creative ideas and solutions. It is therefore plausible that *creative* movement and *creative* thought processes share functional similarities which reinforce the utility of embodied cognition in this domain.

Practicing and discovering creative movements may further enhance how creative ideas are generated. Building on functional similarity, the process of exploring the movement solutions an environment offers and exploiting novel, functional movements may translate to and improve how individuals explore and generate novel ideas. Indeed, fluid, unstructured and unconstrained (in a way creative) movement has been suggested to serve as a pathway to fluid, distributed thought, which may parallel creative thought processes (Leung et al., 2012; Slepian and Ambady, 2012; Kuo and Yeh, 2016; Zhou et al., 2017). While the link between movement and cognitive creativity has not been thoroughly considered in the literature, in the embodied creativity domain, emphasis should be placed on designing a training environment that offers novel affordances and invites individuals to explore how they might effectively generate creative movement. Considering the prominence of creativity within various physical domains (e.g., dance and sport), we speculate that this approach may have a favorable impact on creative cognition as well.

CREATIVE MOVEMENT

Creative movement is generally defined as a functional and original movement solution to achieve a task goal (Memmert and Perl, 2009; Hristovski et al., 2011; Orth et al., 2017). From an ecological dynamics approach, movement emerges from a continuous, cyclical, and prospective coupling of perception, cognition, and action, situated in the dynamic performer-environment interaction (Gibson, 1979; Davids et al., 1994; Warren, 2006). Humans move to perceive what opportunities for action their environment offers (i.e., affordances), perceive affordances to (self) organize their movement, and, cyclically, movement reveals new (flow of) information that specifies affordances (Michaels and Beek, 1995; Chemero, 2003; Fajen, 2005; Bruineberg and Rietveld, 2014). Across an affordance landscape, some affordances stand out and invite performers to certain actions (Bruineberg and Rietveld, 2014; Rietveld and Kiverstein, 2014; van Dijk and Rietveld, 2016). For example, a variety of actions can be performed in a school gym, but a ball on the ground and a goal create intentionality for most children to perform a kicking action. Creative movement however emerges overtime and from a transformational process, involving search, exploration and discovery of novel, and functionally efficient actions (Hristovski et al., 2009; for an example in dance improvisation, see Kimmel et al., 2018; Rudd et al., 2020). Hypothetically, humans have both opportunities and capacities to perform different creative movements to achieve the same or different goals. In fact, a rich landscape of affordances constantly surrounds a moving organism, offering a vast array of movement options (Bruineberg and Rietveld, 2014; Rietveld and Kiverstein, 2014), and the human body is a multi-stable, degenerate system that can flexibly switch between different movement patterns (Kelso, 2012; Seifert et al., 2013). The more enriched an environment and greater the action capabilities of an individual the higher the possibilities for innovation through interaction creating an abundance of movement options (Bruineberg and Rietveld, 2014; Rietveld and Kiverstein, 2014).

Supporting and teaching creativity to emerge is however a tricky affair as people, typically, are attracted to and utilize affordances to guide their movement that are commonly accepted in their society (Rietveld and Kiverstein, 2014; van Dijk and Rietveld, 2016). In other words, they follow the norm, do what is typically done, and act within their comfort zone. For example, if a teacher turns on the music during a physical education (PE) class and ask children to dance, anecdotally, they will all likely perform a handful of dance movements, which correspond to the current "hits," e.g., "the floss dance." Teaching creativity requires designing learning environments that offer a broad range of task-relevant affordances as well as a safe space to encourage an individual to continuously explore functional and novel movement solutions. For example, in teaching the high jump, the introduction of foam-safety mats allowed for safe exploration and practice of landing on the back, which promoted the emergence of a new creative and highly functional movement solution – the "Fosbury Flop." In this sense, teachers are considered environmental designers that can influence learners' intention and invite them to explore and discover a range of movement solutions. This safe and non-judgmental (i.e., no correct technique) exploration of an affordance landscape will see individuals experimenting and creating a wide range of movement solutions to the task (Rasmussen et al., 2017; Woods et al., 2020). Keeping with the dance example and pertinent to this paper, the teacher's instructions should frame a child's intentionality to be open to new dance movements, explore different movement sequences, and add variability into their movements with the music, and in doing so moving away from the floss dance. Common strategies currently used are instructions (e.g., "avoid imitating your peers" in a class setting) and manipulation of task and environmental constraints (e.g., rules and equipment; Hristovski et al., 2011, 2012; Torrents et al., 2015, 2016). In summary, creative movement emerges when a performer perceives and utilizes novel affordances, and a learning environment (including framing of individual's intentionality) that encourages perceptual-motor exploration promotes creativity. Here, we provide a theoretical rationale to promote the development of creative movement using movement sonification.

MOVEMENT SONIFICATION

Movement sonification may represent an innovative strategy to enrich a learning environment and promote the development of movement creativity. It consists of mapping a movement parameter into sound, and depending on how the specified movement parameter (s) change (s) a sound is triggered or changes characteristics, e.g., frequency and amplitude (Effenberg, 2005; Hermann et al., 2011; Dyer et al., 2017). For example, a sound tone is triggered when a joint angle exceeds a certain threshold (e.g., Boocock et al., 2019) or a music melody is progressively distorted in reference to the amplitude of a joint angle increase (e.g., Lorenzoni et al., 2019). Given the inherent tight link between movement and sound (Stanton and Spence, 2020), movement sonification has recently gained an increased interest in the motor learning and control field as a suitable strategy to deliver augmented feedback (Sigrist et al., 2013; Dyer et al., 2015). In fact, sonification of a movement parameter has been shown to enhance a multimodal perception of intrinsic feedback (e.g., proprioceptive information) and the dynamics of perception-action coupling (Dyer et al., 2017), typically resulting in improved motor learning and performance (for reviews, see Effenberg et al., 2016; Schaffert et al., 2019). Here, we discuss how movement sonification can also be used to influence movement creativity.

Movement sonification can be used to enhance how a performer perceives the (currently) utilized affordances, directing them to novel affordances, and promote a change in a learner's intentionality toward an exploration of a new, functional, and creative movement. Once a learner is aware of the currently used affordances and changes their intentionality toward trying out new movements, they start a movement exploration process that will promote the emergence of movement creativity. The exploration process will perturb the performer-environment dynamic (e.g., learner and music) and will shape new affordances for novel creative movement. A learner can spontaneously change their intention ("I hear the sound changing as I change my moves, I should experiment with these movements and sounds") or teacher's should educate the learner's attention toward the environmental shift caused by their movement, thus supporting the learner's knowledge of the environment (Gibson, 1979). Importantly, movement sonification *per se* does not shape novel affordances but invites learners to explore a broad range of new movements, which in turn will create new affordances. In short, the key component for movement creativity to emerge is a learner's exploration of movement options, and movement sonification can promote this process. These mechanisms are discussed hereafter, and their application is exemplified in a creative dance intervention for children during PE classes, which represents a suitable learning context for creative movement.

As previously mentioned, a critical component for creative movement to emerge is a learner's perceptual openness and attunement to the rich landscape of affordances surrounding them (Rietveld and Kiverstein, 2014). A performer should be aware of the currently used affordances and be invited to find new solutions. In this context, movement sonification can enhance one's awareness of the movement solutions they are currently adopting and support a change in their intentionality toward trying different (functional) movements. Previous research has shown that sonification increased dancers' awareness of the "movement vocabulary" they were using and movement sequences they were performing and facilitated their exploration of novel movement patterns (Diniz et al., 2012; Françoise et al., 2014; Wood et al., 2017). With this, we are not suggesting that movement sonification should direct a performer's attentional focus to their movement (which has been shown to be detrimental for motor performance and learning; Wulf, 2013), but instead it should enhance a performer's perception of how they are currently using the variety of movement possibilities the environment is offering. In short, movement sonification will promote an enhanced performer's attunement to the dynamics of task-environment they are embedded in. Keeping with the previous dance example, if a PE teacher turns on music and asks their children to create dance moves, they likely will replicate current dance "hits" (i.e., a handful of movements). To encourage children to find new movement, some parameter of the music (such as frequency and tempo) can be mapped onto children's movement and change according to how they find new movements. An initial assessment of children's typical dance moves is needed to set a child's movement signature as reference, and a selected music parameter can change when child deviates from their movement signature. If necessary, to educate a child's attention toward knowledge of the environment, the teacher could briefly explain how a child's movement can change music, and invite their students to explore movements to manipulate and play with the speed and tempo of the music through their movements. This will enhance children's perception of their currently adopted movement (i.e., music does not change if they perform the usual movement) and invite them to try new movement (i.e., music changes).

Movement sonification is mapped within the coupling of perception and action, and represents an informational constraint that can facilitate releasing a movement's degrees of freedom (hence creativity, see Hristovski et al., 2011; Torrents et al., 2020). From the cyclical coupling of perception and action, action "creates" new information for further action, and sonification can amplify this newly "created" information and encourage learners to perceive and exploit this information. This can be particularly relevant for sequences of movements and movement improvisation (e.g., in dance), whereby each movement is regulated on the (information about) previous movement. In this sense, movement sonification facilitates a learner's perception of the "novel" affordances. Previous research in dance improvisation has shown that sonification enhanced participants' variety of novel movements relative to a no-sonification condition (Yamaguchi and Kadone, 2017) and supported the creation of Japanese dance sequences (Dahlstedt and Dahlstedt, 2019). Keeping with the dance example, the PE teacher can ask their children to create dance movement sequences, but this time there is not a predefined music and children's movement will create music. Each child's movement is mapped onto a different sound, and children are instructed to create music by combining different movements (for an example of this procedure, see Landry and Jeon, 2017). They are also encouraged to create different combination of sounds by creatively combining movements. By doing this, children have to continuously perceive each movement they perform and regulate the next movement accordingly. This approach will also promote exploration, movement fluency, and functionality, as the produced sound will encourage children to move fluently to "create" a nice and smooth music.

Movement sonification can also motivate performers to pursue new creative movement and increase enjoyment especially in children. Sonification will readily "tell" and reward a performer when a new movement is created and it will encourage children to explore movement in a fun and safe environment. They can play with their movement repertoire *via* the different sounds they can create. Another important aspect worth mentioning is that movement sonification puts performers in charge of the task they are performing. This can likely promote self-regulation (key in embodied cognition, Diamond, 2016; Diamond and Ling, 2020), especially in children, as they have to self-regulate their behavior to keep up with the task and keep the task engaging and fun. Movement sonification will "tell" them straight away if they are disengaging with the task. Lastly, movement sonification can be mapped on movement of each individual, even in a classroom setting, thus it can support the individuality and non-linearity of learning (Newell et al., 2001; Pacheco et al., 2019). The learning intervention will be individualized and will follow the non-linear movement improvement, aligning with the principles of nonlinear pedagogy (Chow et al., 2007, 2015).

Teachers and coaches play a pivotal role in guiding their students toward using sonification for creating original movement. As previously mentioned, they should oversee the creativity process and, if necessary, guide attention to specify knowledge of the environment (Gibson, 1979), this can be done through careful instructions, encouraging their students to explore different and novel movement possibilities. This needs to be done in conjunction with individualizing the movement parameter(s) to sonify. A variety of parameters can be sonified and various sonification techniques have been proposed in the literature (e.g., Hermann et al., 2011; Siegel, 2012). It is beyond the scope of this article to discuss this issue in detail, but we can say that the selection of parameter(s) to sonify is context specific and depends on the teacher's goal and possibilities (Landry et al., 2014). In a school PE context (as per our example), financial constraints and limited technological expertise may restrict sonification options. However, simple and relatively low-cost strategies can still be implemented. For example, accelerometers placed on pupils' joints (e.g., wrists and ankles) can sonify movement acceleration, difference in acceleration between body parts, or parts of the body involved in the movement (e.g., see Françoise et al., 2014; Yamaguchi and Kadone, 2017). In such a scenario, the teacher can invite students to explore different movement speed and fluency, and change how they activate the different body parts. Ultimately, schools should not bear the cost of developing a suitable strategy. We presented a principled approach that can underpin the design and development of sonification techniques to influence movement creativity, and we hope that inter-disciplinary collaboration between universities and industry can support schools in the process, as advocated through a transdiscplinary approach by Vaughan et al. (2019).

CONCLUSION

In this article, we argue for an embodied approach to creativity that emphasizes the important relationship between movement and cognition in the development of creativity. The development of technologies such as sonification offers new opportunities for designing learning environments that promote creativity. We provided a rationale for using movement sonification to promote creative movement and exemplified its use in creative dance for children. Our approach allows to better understand the embodied nature of creativity as the sonification is "embodied in perception and action" providing a rich landscape for future research to explore creativity. The tasks that can be created can be cognitively challenging and involve a high degree of problem solving that may transfer to more divergent and creative thinking in the classroom.

We contend that learning to explore original dance sequences using movement sonification may provide a meaningful link between creative movement and creative cognition. This association is predicated, in part, on functional similarities between novel actions and thought, such that the process of learning how novel movement parameters map onto sound may facilitate perception-action coupling in novel contexts sharing similar features. In this vein, children may be more inclined to exploit environmental affordances in the classroom after experiencing the self-regulatory process of creating music through physical movement. This may mean that children become more likely to rely on their minds *and* bodies as tools for creative thinking and exploration, such as using their whole bodies to learn the shapes of letters and numbers or acting out scenes from history and science lessons as a strategy for learning new concepts. Future empirical work is necessary to investigate whether and how transfer may unfold from movement sonification to diverse creative problem-solving contexts.

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.

AUTHOR CONTRIBUTIONS

All authors conceptualized, drafted, edited, reviewed, and approved the manuscript.

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Altered Brain Functional Connectivity Density in Fast-Ball Sports Athletes With Early Stage of Motor Training

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The human brain shows neuroplastic adaptations caused by motor skill training. Of note, there is little known about the plastic architecture of the whole-brain network in resting state. The purpose of the present study was to detect how motor training affected the density distribution of whole-brain resting-state functional connectivity (FC). Resting-state functional magnetic resonance imaging data was assessed based on a comparison of fast-ball student athletes (SA) and non-athlete healthy controls (NC). The voxel-wise data-driven graph theory approach, global functional connectivity density (gFCD) mapping, was applied. Results showed that the SA group exhibited significantly decreased gFCD in brain regions centered at the left triangular part of the inferior frontal gyrus (IFG), extending to the opercular part of the left IFG and middle frontal gyrus compared to the NC group. In addition, findings suggested the idea of an increased neural efficiency of athletes' brain regions associated with attentional–motor modulation and executive control. Furthermore, behavioral results showed that in the SA group, faster executive control reaction time relates to smaller gFCD values in the left IFG. These findings suggested that the motor training would decrease the numbers of FC in IFG to accelerate the executive control with high attentional demands and enable SA to rapidly focus the attention to detect the intriguing target.

Keywords: athlete training, global functional connectivity density, resting-state functional magnetic resonance imaging, attention, neuroplasticity

INTRODUCTION

The brain of skilled elite athletes who have improved sport performance reveals neuroplastic adaptations caused by motor skill training (Gao et al., 2019; Chen et al., 2020; Jung et al., 2020). It has attracted special attention from researchers exploring how and where the structural and functional plasticity of the brain occurs in the course of motor skill training using imaging techniques [e.g., functional magnetic resonance imaging (fMRI) and functional near infrared spectroscopy (fNIRs)] (Crawford et al., 2019; Yu et al., 2020; Yue et al., 2020a,b). In particular, fMRI is widely accepted as an effective method to help researchers to understand the physiological mechanisms of brain plasticity via motor training; furthermore, findings might be practically meaningful for improving athletic performance (Gao et al., 2019; Zhang et al., 2019). However, it is largely unknown how brain functions change in the process of motor training (Lappi, 2015). Some researchers attempted to investigate the difference in brain activity between athletes and non-athlete controls (NC) during certain tasks (Gao et al., 2019), with different regions of task-induced activation between the two groups that are being reported. For instance, in the visual smooth pursuit task, football players showed greater activation in the oculomotor region of the cerebellar vermis and areas of the frontal eye fields than NC, suggesting visual motor skill is required for elite football players to successfully execute complex movement during games (Kellar et al., 2018). In addition, enhanced inferior parietal/frontal gyrus activity has been proposed in basketball players anticipating a free-throw task (Wu et al., 2013). Previous research suggested that when familiar sports environmental sounds surrounded, elite athletes tend to have greater activation in somatosensory regions but less activation in brain regions, which associated with perception and motor planning and processing (Woods et al., 2014). Except for the aforementioned results, a decreased brain activation in athletes (e.g., archery and table tennis) was reported across various cognitive tasks (e.g., mental rehearsal and visual–spatial task) compared to non-experts (Chang et al., 2011; Guo et al., 2017).

Resting-state fMRI (rsfMRI) is the commonly used method in the human brain map to evaluate intrinsic spontaneous fluctuations in the blood oxygen level-dependent (BOLD) signal in the resting or task-free state (Gao et al., 2013). This innovative and effective method was widely used in previous studies to investigate intrinsic brain plasticity or regional interaction induced by motor training. A study which implemented seed-based functional connectivity (FC) in distance runners shows increased connectivity between the fronto-parietal network and brain regions for execution functions compared to non-expert runners (Raichlen et al., 2016). These functional alterations in fronto-parietal connectivity were also found in badminton athletes (Di et al., 2012; Xu et al., 2016). In addition, similar results are found in elite karate players, suggesting brain areas associated with movement planning and visual perception having increased connectivity (Duru and Balcioglu, 2018). Our recent study using seed-based stepwise FC showed that fast-ball athletes were reported with a significantly smaller optimal connectivity distance from seed regions to the dorsal attention network (DAN) and larger optimal connectivity distance to the default mode network (DMN; Gao et al., 2019). Given the evidences above, changes in resting-state-FC brain plasticity occur in different brain areas across various sport events.

However, seed-based methods involved with the *a priori* selection of appropriate seed regions are unable to fully characterize the brain functional connectome as well as get a whole picture on the plastic architecture of the whole-brain network (Joel et al., 2011). Recently, functional connectivity density (FCD) mapping, a voxel-wise data-driven graph theory approach, has been established to determine the density distribution of whole-brain resting-state FC (Tomasi and Volkow, 2011; Huang et al., 2018). It measures the number of functional connections of a given voxel with the remaining voxels in the whole brain. The brain regions with high FCD values are considered as functional hubs of the human brain, which play a very important role in brain function (Tomasi and Volkow, 2011). Thus, this approach is a reliable and effective method and has been increasingly accepted in research detecting biomarkers of neuropsychiatric disorders through resting-state functional network alterations, including schizophrenia (Huang et al., 2018), major depressive disorder (Zhang et al., 2016; Zou et al., 2016), migraine (Gao et al., 2016), and aging brain (Li et al., 2019).

Here, we aimed to explore the neuroplasticity on brain functional organization induced by motor training using the global FCD (gFCD) approach. Fast-ball student athletes (SA) who play badminton, tennis, and table tennis were recruited. In fast-ball sports like badminton, tennis, and table tennis, the players require well-refined hand–eye coordination and visuospatial ability to achieve improved sports-related cognitions such as perception, focus, anticipation, planning, and fast responses (Di et al., 2012; Wolf et al., 2014). We started with an assumption that the fast-ball athletes would show changes in FC architecture in brain regions related to the visual attention and visual–motor coordination. To test whether the brain gFCD values relate to attentional processes, all subjects were asked to perform a revised attention network test (ANT) processing. The relationships between gFCD and reaction time of each attention subnetwork of alerting, orienting, and executive control were also investigated.

MATERIALS AND METHODS

Participants

Forty-two SA majoring in fast-ball sports (badminton, tennis, and table tennis) were recruited from Chengdu Sport University. All SA were required to pass the college entrance examination for sports majors in Sichuan province of China before entering Chengdu Sport University. The examination consisted of 40 points of the sport-specific test and 20 points of three physical fitness events, including 100-m run, standing triple jump, and standing shot put. The full mark of all test items is based on or slightly higher than the Standard of Technical Grade of Athletes issued by the General Administration of Sport of China. For example, the full mark of 100 m is 11.54 s, and the total score of all four test items has to exceed 85 points. After entering Chengdu Sport University, SA have been engaged in the fast ball-specific training. The training duration was less than 3 years, and the training frequency was less than 25 h per week. Thirty-nine NC with matched age, gender, and education level were also recruited. Except the sports-required course in the university, the NC group spent no more time on physical activity. All participants were tested handedness using the Chinese version of the Edinburgh-Handedness Questionnaire (coefficients > 50) (Oldfield, 1971), and all showed right-handedness. Participants had no history of neurological or psychiatric diseases or concussions. The study protocol was approved by the research ethical committee of School of Life Sciences and Technology, University of Electronic Science and Technology of China. Participants were provided written informed consent prior to any assessment.

Data Acquisition

Magnetic resonance imaging (MRI) images were acquired on a 3.0 T GE Signa MR750 system (GE Healthcare, Milwaukee) with an 8-channel phased array head coil. High-resolution 3D T1-weighted anatomical images were obtained in axial orientation using a 3D spoiled gradient-recalled (SPGR) sequence. The acquisition parameters were as follows: TR = 5.97 ms, TE = 1.96 ms, field of view (FOV) = 240 mm × 240 mm, flip angle = 12°, matrix size = 512 × 512, 156 slices, and voxel size = 1 mm × 1 mm × 1 mm. Resting-state fMRI images were acquired using a gradient-recalled echo planar imaging (EPI) sequence. The parameters were TR = 2000 ms, TE = 30 ms, FOV = 220 mm × 220 mm, flip angle = 90°, matrix size = 64 × 64, 43 transverse slices without a slice gap, voxel size = 3.75 mm × 3.75 mm × 3.2 mm, and a total of 266 volumes for each subject. During the scan, the subjects were instructed to lie down with their eyes closed, not to think of anything in particular, and not to fall asleep. Padded foams were used to restrict head motion, and earplugs were used to attenuate scanner noise.

Data Preprocessing

Conventional fMRI data preprocessing was performed using Data Processing Assistant for Resting-State fMRI software (DPARSF, Advanced Edition, V4.5).[1] The first 10 volumes of each subject were discarded to ensure steady-state longitudinal magnetization. The remaining 256 resting-state fMRI images were first corrected for the acquisition time delay between different slices and then realigned to the first volume to correct for head motion. We required that the transient movement during the scanning was no more than 1.0 mm of translation and 1.0° of rotation. The images were further spatially normalized into a standard stereotaxic space at 3 mm × 3 mm × 3 mm, using the EPI template in the Statistical Parametric Mapping software (SPM8). The images were not smoothed to avoid introducing artificial local spatial correlations. Images were then linearly detrended and were corrected using linear regression to remove the possible spurious variances including 24 head-motion parameters, averaged signals from cerebrospinal fluid, and white matter. The residuals of these regressions were temporally band-pass filtered ($0.01 < f < 0.08$ Hz) to reduce low-frequency drifts and physiological high-frequency respiratory and cardiac noises. Finally, scrubbing with the interpolation method was used to remove the bad points of the data. Since FC analysis is sensitive to gross head motion effects (Power et al., 2012), the mean frame-wise displacement (FD) was calculated to further determine the comparability of head movement across groups. The largest FD obtained from the subjects was less than 0.2 mm (which was 0.178 mm).

[1] http://www.restfmri.net/forum/

Global Functional Connectivity Density Analysis

Global functional connectivity density is defined as the number of statistically significant FCs between a given voxel and the rest of voxels across the whole brain in a binary network (Tomasi and Volkow, 2010). It is capable of quantifying the importance/centrality of a given voxel within the whole-brain network (Tomasi and Volkow, 2010). The voxel-wise gFCD maps were computed by an in-house program coded in MATLAB (The MathWorks, Natick, MA) according to the approach introduced by Tomasi and Volkow (2010). Briefly, we calculated the Pearson's correlation (r) between brain voxels that limited in a gray matter mask based on the automated anatomical labeling (AAL) atlas to obtain a whole-brain FC map at the voxel level. Two voxels were considered to be connected if their Pearson's correlation coefficient of the two voxels was greater than a given correlation threshold $Tc = 0.6$ according to the significant level of $p < 0.01$ (Bonferroni multiple correction), in order to eliminate the weak correlation which may be caused by noise (Tomasi and Volkow, 2010; Huang et al., 2018). Here, the significant level was set for testing the hypothesis of no functional connection against the alternative that there is a functional connection (non-zero correlation). The value of gFCD was defined of the global number of functional connections n_i, between voxel i and all other voxels in the brain. For each participant, gFCD maps were further standardized by the total number of edges in the whole brain (Li et al., 2018) and were spatially smoothed with full-width at half-maximum (FWHM) = 8 mm to minimize the individual overall differences of gFCD values (Tomasi and Volkow, 2011).

The Attention Network Test

To test whether the altered FC network architecture relates to attentional processes, all subjects were asked to perform a revised ANT (Wang et al., 2016), as shown in **Figure 1**. Briefly, the stimuli were presented via E-Prime 2.0 (Psychology Software Tools,

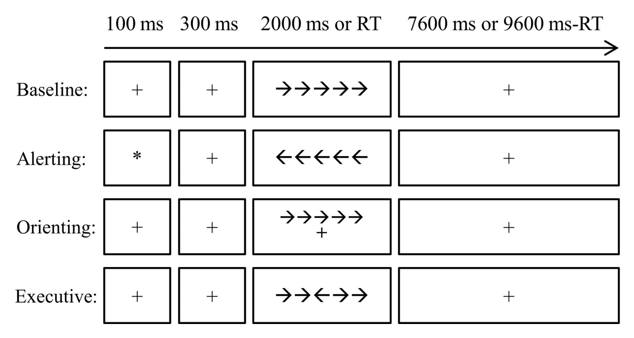

FIGURE 1 | The diagram for the attention network test (ANT) procedure. The four conditions, i.e., baseline, alerting, orienting, and executive control, were arranged in separated blocks. Each trial started with a cue (the alerting condition) or a fixation with 100 ms. After a 300-ms interval, the target was presented for 2,000 ms or disappeared after one key was pressed. A fixation was then presented until the end of that trial. Each trial lasted for 10 s. RT, reaction time.

Inc[2]) on a Lenovo PC. Responses were collected via Q (for left targets) and P (for right targets) on the keyboard. All participants completed four blocks (alerting block, orienting block, executive control block, and baseline block) of the ANT. The order of the four blocks was counterbalanced across subjects. Each block took 424 s, which contained a buffer time of 4 s, two practice trials of 10 s, and 40 experimental trials of 10 s. As shown in **Figure 1**, each trial began with a fixation or cue for 100 ms which was followed by a 300-ms fixation. After that, a target (congruent or incongruent, central, or spatial) appeared for 2000 ms or until the participant pressed a key. Lastly, another fixation was presented to ensure that the overall time of one trial was 10,000 ms (0.1 Hz). The subjects were asked to judge the direction of the third arrow (the central one) by pressing Q if it points to the left and P if it points to the right. The attention network scores (ANSs) were computed to measure the reaction time of each attention subnetwork of alerting, orienting, and executive control compared to the baseline (Wang et al., 2016).

Statistical Analysis

We used two-sample *t*-test analysis to compare the group differences of gFCD between the two groups. Age, gender, and education were considered as covariate variables. The statistically significant threshold of the gFCD was set for multiple comparisons at the cluster level with $p < 0.05$ (AlphaSim corrected). This correction was conducted using the DPARSF software.

To investigate whether the altered gFCD was associated with the behavioral reaction time of each attention subnetwork of alerting, orienting, and executive control, relationships between gFCD values in regions showing significant group differences and the reaction time of the three attention subnetworks were further detected by partial correlation analysis. The partial correlation analysis was performed for the SA group and the NC group, separately, with age and gender as confounding factors.

RESULTS

Demographic Data

The demographic data of the recruited subjects are shown in **Table 1**. The athlete group and the control group did not differ significantly in age (Mann–Whitney U-test, $p = 0.17$), gender (Pearson χ^2 test, $p = 0.35$), education (Mann–Whitney U-test, $p = 0.58$), or mean FD (Mann–Whitney U-test, $p = 0.94$).

gFCD in Athletes and Controls

Figure 2 shows the spatial distribution maps of the average gFCD in the SA group and the NC group, respectively. In both the SA and NC groups, the prefrontal cortex, posterior cingulate cortex, precuneus, and occipital cortex had relatively high gFCD values, as reported in previous studies (Tomasi and Volkow, 2010; Luo et al., 2014; Huang et al., 2018). **Figure 3** (left) shows the significantly different gFCD between the groups ($p < 0.05$, AlphaSim corrected). The SA group exhibited significantly decreased gFCD in brain regions centered at the left triangular part of the inferior frontal gyrus (IFG), extending to the left opercular part of the IFG and middle frontal gyrus (MFG) compared to the NC group. **Table 2** presented the Montreal Neurological Institute (MNI) coordinates of peak voxels and statistical *t*-values of the brain regions with significantly different gFCD between the two groups. The positive *t*-values represented that the NC group had higher gFCD values than the SA group. No significantly increased gFCD in the SA group compared with the NC group was found.

ANT Scores and Relationships With gFCD

Figure 3 (right) shows the significant correlations between the gFCD values and the reaction time of executive control in the SA group. In the SA group, the gFCD values in the left triangular part of IFG showed significant positive correlations with the executive control reaction time. In the NC group, subjects had relatively low values in reaction time, and the within-group dispersion of the reaction time was relatively small. The significant correlation between the gFCD values and the reaction time was not detected in the NC group.

DISCUSSION

The frontal cortex is one of the most crucial areas related to high-level functional integration (Woods et al., 2014). The inferior and middle frontal cortex especially contributed to the visual attention modulation and executive functions (Woods et al., 2014; Guo et al., 2017). In the task research in athletes, expert athletes had less activation in IFG and MFG when listening to familiar sports environmental sounds, suggesting the neural efficiency in these brain regions associated with perception and motor planning and processing (Woods et al., 2014). During the motor reaction and the visuo-spatial tasks, formula racing-car drivers recruited distributed networks including the middle and inferior frontal cortices, which devoted to executive functions (Bernardi et al., 2013). However, professional drivers recruited these regions to a significantly smaller extent as compared to naïve subjects (Bernardi et al., 2013). As support, table tennis athletes perform the visuo-spatial task with less brain activation in bilateral MFG than non-athletes (Guo et al., 2017). A similar finding was also observed in expert hockey players, suggesting neural efficiency in these brain regions for action decision as they were presented videos for shooting a puck toward a hockey goal (Olsson and Lundstrom, 2013). However, there were controversial results in some tasks. For instance, an increased activity in the inferior parietal lobule and IFG was detected in basketball athletes performing a free-throw task (Wu et al., 2013). Therefore, the task-related results demonstrated IFG and MFG as functional hubs of visual motor integration, motor control, and executive functions. In addition, the results suggested their functional plasticity induced by motor skill training.

The rsfMRI results are independent of task. The task-free approach can explore the intrinsic neural plasticity induced by

[2]http://www.pstnet.com

TABLE 1 | Demographics of the subjects.

	Age (years)	Gender (female/male)	Education (years)	Training time (h/week)	Duration (years)	Mean FD (mm)
SA (*n* = 42)	20.43 ± 0.59	12/30	14.57 ± 0.67	17.17 ± 0.83	1.95 ± 0.08	0.08 ± 0.02
NC (*n* = 39)	20.33 ± 1.33	15/24	15.05 ± 1.43	–	–	0.08 ± 0.03
P value	0.1736[a]	0.3454[b]	0.5803[a]	–	–	0.9363[a]

Data are presented as mean ± SD. SD, standard deviation; FD, frame-wise displacement; NC, non-athlete controls; SA, student athlete. [a]Obtained using Mann–Whitney U-test. [b]Obtained using the Pearson χ^2 *test.*

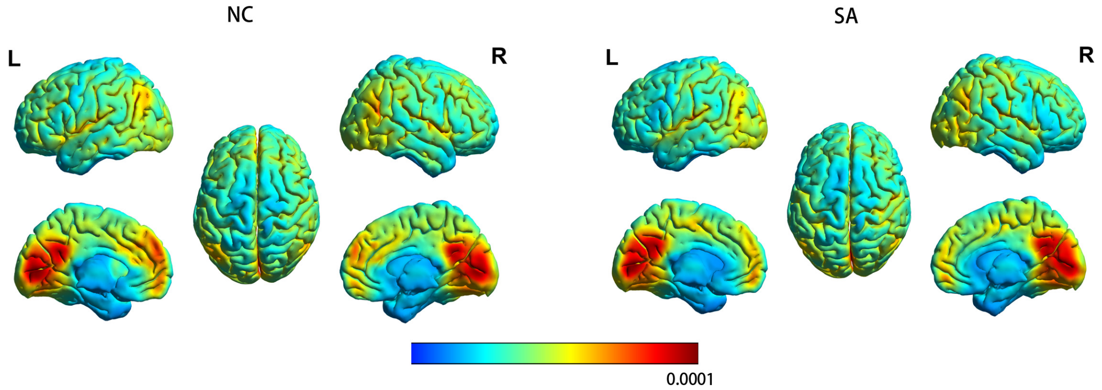

FIGURE 2 | The spatial distribution maps of the average gFCD maps for the SA group and the NC group. For each participant, the gFCD value of each voxel was standardized by the total number of edges in the whole brain. L, left; NC, non-athlete control; R, right; SA, student athlete.

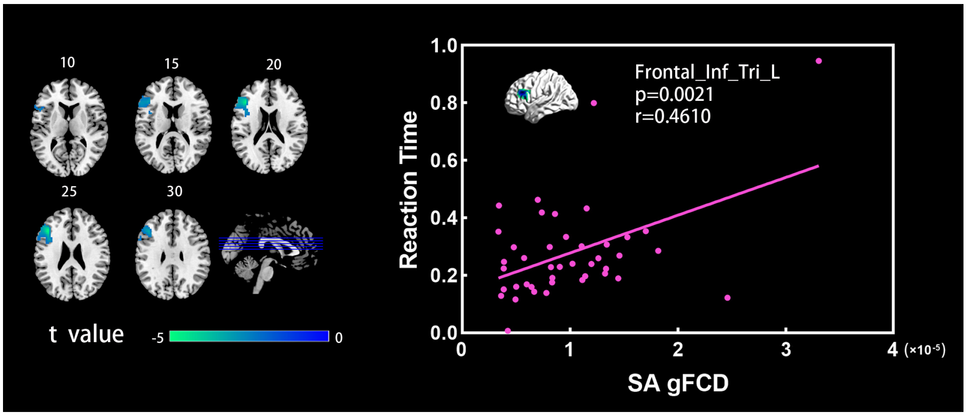

FIGURE 3 | (Left) Brain regions showing significant differences between the SA and NC groups in the gFCD analysis (two sample *t*-test, $p < 0.05$, GRF corrected). Numbers above each image refer to the *z*-plane coordinates of the MNI space. **(Right)** Significant correlation between reaction time and gFCD values in the SA group. Frontal_Inf_Tri_L, left triangular part of inferior frontal gyrus.

TABLE 2 | Brain regions showed significantly different gFCD between the athlete group and the control group.

Brain regions	Hem	Peak coordinates	Cluster size	*T*-value
Inferior frontal gyrus, triangular	L	(−39,27,24)	328	5.63
Inferior frontal gyrus, opercular	L	(−57,27,18)	68	3.83
Middle frontal gyrus	L	(−54,36,21)	144	3.72

motor skill training. There has been local seed-based FC analysis, which showed altered FC between the athlete group and controls within the left frontoparietal network (Di et al., 2012). In the athlete group, an enhanced FC between the left superior parietal lobule and left MFG (BA6) was detected, whereas a lower FC between the left superior parietal lobule and the left MFG (BA9) was observed compared to the control group (Di et al., 2012). In addition, previous research was found that distance runners exhibited enhanced connectivity between the right parietal cortex and MFG (Raichlen et al., 2016).

Global functional connectivity density is a powerful framework to characterize the FC architecture within the whole-brain network without any prior hypothesis (Tomasi and Volkow, 2011). From the point of view of the whole-brain resting-state FC, our results showed decreased gFCD values in the left IFG and MFG in the fast-ball SA group compared to the NC group. This is a distinct but complementary information on the brain plasticity caused by motor skill training in fast-ball SA. Such results demonstrated reduced connections between these brain regions and the remaining brain voxels in the SA group. The findings were consistent with the previous research, regardless of skilled groups, such as racing-car drivers (Bernardi et al., 2013), table tennis players (Guo et al., 2017), basketball players (Pi et al., 2019), golfers (Milton et al., 2007), and musicians (Haslinger et al., 2004; Meister et al., 2005). The possible explanation could be that athletes' brain might exhibit an improved neural efficiency in the brain regions associated with attentional-motor modulation and executive control along with a reduced "resource consumption" (Rypma and Prabhakaran, 2009; Bernardi et al., 2013; Guo et al., 2017; Sommer et al., 2018; Zhang et al., 2019).

Importantly, we further detected a positive correlation between gFCD values in the left triangular part of IFG and reaction time of the executive control in the SA group. Of the three attention subnetworks, the executive control network is very useful for producing top-down regulation and thus is related to executive control (Petersen and Posner, 2012). This system was presented under the heading of target detection (Petersen and Posner, 2012). It is related to the limited capacity of the attention system, and to awareness itself, and has often been called focal attention (Petersen and Posner, 2012). Fast-ball sport events require athletes to execute actions in a short time (Ermutlu et al., 2015), in terms of well-refined hand–eye coordination and visuospatial ability to achieve enhanced perception, concentration, anticipation, planning, and fast response requirements (Di et al., 2012; Gao et al., 2019). Our results suggested that faster executive control reaction time was associated with smaller gFCD values in the left triangular part of IFG. The behavioral results further supported that in the SA group, shorter reaction time of executive control was associated with smaller gFCD values, which referred to the numbers of FC between a given voxel and the rest of voxels across the whole brain. The findings implied that motor skill training results in a decrease in the number of FC in the left triangular part of IFG, which athletes are interested in developing reaction capacity, movement planning, and execution with high attentional demands, and focus the attention to the target detection (Wolf et al., 2014). Of note, sample size was relatively low in the present study, and only the student-athletes who were trained in fast ball of badminton, tennis, and table tennis were recruited. Our findings only limited to the fast-ball sports athletes with early stage of motor training.

CONCLUSION

Using resting-state functional imaging techniques and graph theory approach, the present study revealed that compared with the NC group, the SA group exhibited significantly decreased gFCD in IFG and MFG. As supportive of the behavioral data, faster executive control reaction time was associated with smaller gFCD values in the left triangular part of IFG in the SA group. The findings supported the idea of an increased neural efficiency of athletes' brain in the brain regions associated with attentional-motor modulation and executive control and implied the training-induced neuroplasticity occurring in these brain regions. In addition, our findings were based on the resting-state brain functional network, which was independent of specific tasks. The neural mechanisms of functional adaptations in the athletes' brain that made their exceptional performance possible might have potential applications in designing optimal sports coaching methods, in overcoming learning disabilities, and in neurological rehabilitation (Lappi, 2015).

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study protocol was approved by the research ethical committee of School of Life Sciences and Technology, University of Electronic Science and Technology of China. 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

CY, NL, and QG contributed to the conception and design of the research. MZ, JG, HW, and ML collected the data. ML, SZ, and JZ applied the statistical analysis. NL and CY analyzed and interpreted the data. CY, NL, and QG wrote the manuscript. QG and HC edited the manuscript. QG was responsible for the overall project. QY edited and modified the manuscript. All authors contributed to the article and approved the submitted version.

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Comparing the Psychological Effects of Meditation- and Breathing-Focused Yoga Practice in Undergraduate Students

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Objectives: The present study aimed to compare the psychological effects of meditation- and breathing-focused yoga practice in undergraduate students.

Methods: A 12-weeks yoga intervention was conducted among a group of undergraduate students enrolled in four yoga classes at an academically prestigious university in Beijing, China. Four classes were randomized to meditation-focused yoga or breathing-focused yoga. A total of 86 participants finished surveys before and after the 12-weeks intervention, measuring work intention, mindfulness, and perceived stress. The repeated-measure multivariate analysis of covariance (MANCOVA) followed by univariate analyses were conducted to examine the differences in work intention, mindfulness, and stress between the two yoga intervention groups over the semester, after controlling for age and gender.

Results: The repeated-measure MANCOVA revealed significant group differences with a median effect size [Wilks' lambda, $\Lambda = 0.90$, $F(3, 80) = 3.10$, $p = 0.031$, $\eta^2 = 0.104$]. Subsequent univariate analyses showed that students in the breathing-focused yoga group had significant higher work intentions [$F_{(1,\ 82)} = 5.22$; $p = 0.025$; $\eta^2_p = 0.060$] and mindfulness [$F_{(1,\ 82)} = 6.33$; $p = 0.014$; $\eta^2_p = 0.072$] but marginally lower stress [$F_{(1,\ 82)} = 4.20$; $p = 0.044$; $\eta^2_p = 0.049$] than students in the meditation-focused yoga group.

Conclusion: Yoga practice with a focus on breathing is more effective than that with a focus on meditation for undergraduates to retain energy for work, keep attention and awareness, and reduce stress.

Keywords: meditation, breathing, yoga, work intention, mindfulness, stress

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INTRODUCTION

Yoga has different components including postures, movements, meditation, and breathing (pranayama) (Brown and Gerbarg, 2005). The current literature has seen a general consensus of yoga's function in retaining energy and vitality (Bowden et al., 2012; Tyagi et al., 2016) and reducing stress (Riley and Park, 2015). However, little is known of the relative importance of specific components of yoga practices, especially between the most revisited practices of meditation and breathing. Prior research has shown that yoga postures and movements can reduce depression (Carter and Byrne, 2004), but meditation and breathing may be more important to other mental health outcomes including stress and mood (Wheeler et al., 2019), sustained attention (Schmalzl et al., 2018), working memory capacity (Quach et al., 2016) posttraumatic stress disorder, hyperarousal symptoms of sleep disturbance, flashbacks, or anger outbursts (Carter and Byrne, 2004). Moreover, there are evidences for potential differences between meditation and breathing in literature such as the levels of energy (Joshi and Telles, 2009; Zaccaro et al., 2018), attention, and practice difficulty (Brown and Gerbarg, 2009). Thus, the yoga practices of meditation and breathing may function differently in a group of novices with daily mental activities. Our findings may help disclose the nature of yoga components and provide unique guidance for novices with mental work in yoga practices.

Meditation refers to engagement of mental exercise to reach a heightened level of spiritual awareness (Clarke et al., 2018). Meditation is frequently reported to have significant impacts on biological and psychological outcomes. For example, Hendriks (2018) systematically reviewed 11 research studies to examine the effects of yoga meditation on mental health outcomes such as anxiety, depression, stress, and well-being. Meditation also has been studied as an independent practice beyond the scope of yoga such as Buddhist meditation, compassion meditation, mindfulness meditation, and sound meditation. For example, one study showed that meditation was associated with molecular changes in cerebral cortex, prefrontal area, autonomic nervous system, hormones, etc. (Jindal et al., 2013). Meditation is beneficial to cognitive outcomes (Chiesa et al., 2011) and can facilitate stress management (Borchardt and Zoccola, 2018). Specifically, traditional Buddhist meditation programs led to improvement in stress levels and mood (Shonin et al., 2014). Gallegos et al.'s (2017) and Hilton et al.'s (2017) meta-analysis found that mindfulness meditation alleviated the symptoms of posttraumatic stress. Wielgosz et al.'s (2019) review summarized the efficacious applications of mindfulness meditation to many specific domains of psychopathology. Philips et al. (2019) found that sound meditation was better than silence meditation to relax and reduce acute stress.

Breathing as a mental practice has received increasing research interest. During yoga exercise, an individual can practice different patterns of breathing and use specialized techniques to enhance breathing skills such as inhaling deeply into the abdomen, holding the breath at certain parts of the breathing cycle (Brown and Gerbarg, 2009), breathing at varying rates, such as *Sudarshan Kriya* yogic breathing (Brown and Gerbarg, 2005), and/or high-frequency yoga breathing (Joshi and Telles, 2009). Brandani et al.'s (2017) review of 13 studies showed that yoga breathing had a hypotensive effect. Joshi and Telles (2009) found that high-frequency yoga breathing improved selective attention and that breath awareness increased available neural resources by examining event-related potentials (i.e., the P300). Besides biological impacts, breathing, as an important component of yoga practice, can bring upon dramatic psychological and mental benefits. For example, Telles et al. (2011) found that high-frequency yoga breathing significantly decreased the optical illusion, an indicator of improved attention and visual perception. Janakiramaiah et al. (1998) found that yoga breathing functioned as effectively as medical treatment for dysthymic disorder. Shastri et al. (2017) showed that yoga breathing reduced aggression, improved mindfulness, and emotion regulation in undergraduate students. Saoji et al. (2018) also found that yoga breathing enhanced psychological functions such as state mindfulness. Further, Tellhed et al. (2019) found mindfulness mediated the relationship between yoga breathing and mental health. Kizhakkeveettil et al. (2019) summarized that yoga breathing improved the quality of life in individuals with chronic disease by reducing stress, pain, anxiety, depression and fatigue, and improving sleep and emotion. Breathing, as an independent practice, was also found to impact on both autonomic and central nervous systems and psychological status such as increased comfort, vigor and alertness, and reduced symptoms of anxiety, anger, and confusion (Zaccaro et al., 2018).

As summarized above, both meditation and breathing have significant effects on biological and mental outcomes. Despite the usefulness of meditation and breathing, prior research suggests that they may function differently in influencing mental health outcomes such as energy (Joshi and Telles, 2009; Zaccaro et al., 2018) and attention (Brown and Gerbarg, 2009). First, breathing may be related to higher levels of energy, improved attention (Telles et al., 2011), increased available neural resources (Joshi and Telles, 2009), vigor and alertness (Zaccaro et al., 2018), while meditation is usually related to serenity (calmness of mind and body) and relaxation (Koopmann-Holm et al., 2013; Jones et al., 2018; Philips et al., 2019). The increased mental resources and alertness by breathing may stimulate active engagement and improve readiness for tasks, which coincides with work intention. Work intention refers to a guide to purposeful action as it is a mental representation of the behavior an employee chooses to manifest (Ajen and Fishbein, 1980). Intention to continue one's work reflects one's energy level at work, so breathing-focused yoga practice may retain higher levels of work intention than meditation-focused yoga practice. Second, while both meditation and breathing could help achieve mindfulness (Saoji et al., 2018; Wielgosz et al., 2019), breathing may be more practical in achieving mindfulness, a state of consciousness emphasizing attention and awareness in the present (Brown and Ryan, 2003). For example, "many people who try to learn meditation cannot focus their minds," "some find the practices difficult and austere. . .lack the patience to persist," and "trying to meditate while under severe stress sometimes magnifies the subjective sense of distress" (Brown and Gerbarg, 2009, p. 56). However, "one can affect the mind and consciousness through manipulation of the breath" (Brown and Gerbarg, 2009, p. 55). Thus, breathing-focused yoga practice may be more effective to improve mindfulness (i.e., attention and awareness) in a group of yoga novices. Since higher energy levels and mindfulness can help people decrease stress (Tong et al., 2020), breathing-focused yoga practice may be also better to reduce stress than meditation in a group of yoga novices.

Furthermore, a few researches have simultaneously compared the functions of meditation and breathing as yoga components (Ross et al., 2012). Only one study to our knowledge has compared between these yoga practices (Wheeler et al., 2019), which found that yoga manipulation (i.e., poses, breathing, meditation, or listening to a lecture about yoga) was equally effective in reducing anxiety and improving mood but did not affect responses to stressors in a group of yoga novices. This study utilized only a 20-min intervention, which is not a full yoga session and may be not enough to show any different effects of meditation and breathing. A longer intervention with multiple sessions over several weeks is needed to indicate any potential difference and show whether this difference can be retained.

Therefore, the current research aims to explore the potential differences between yoga practices of meditation and breathing in energy and stress-related outcomes in undergraduates, novices with daily mental activities. We hypothesize that breathing-focused yoga practice would be more effective than meditation-focused yoga to promote work intention (1a), and mindfulness (1b), and to reduce stress perception (1c). The varying effects of meditation and breathing may be evident in novice yoga exercisers such as undergraduate students; however, this assumption needs to be tested through empirical evidence. Most undergraduate students have little to no experience of practicing yoga exercise, and they are considered a vulnerable population for mental health (Balon et al., 2015). Engaging in considerable mental work daily, undergraduates would need to accumulate mental resources and alertness at work and to focus. Examining undergraduate students' work intention, mindfulness, and perceived stress, as a function of yoga practices (breathing- or meditation-focused), is important to their academic performance and mental health. We chose to study undergraduate students in this study also because prior yoga research has shown success in recruiting and retaining a relatively large sample of undergraduate students as participants (Shastri et al., 2017; Wheeler et al., 2019); thus we felt confident to recruit a sample of undergraduate students in this study.

MATERIALS AND METHODS

Experimental Design and Procedure

A 12-weeks yoga intervention was conducted among undergraduate students with no prior experience with yoga. Participants were assigned into two groups of meditation- and breathing-focused yoga practice, randomly by class. During the semester, students attended a morning yoga class per week for 12 consecutive weeks following the prescribed intervention. Participants were asked to dress in comfortable clothing and avoid a meal after getting up before attending the class. Baseline surveys were conducted before intervention, and post-training surveys were conducted after the 12th session. Surveys were requested to be finished before leaving the class.

Baseline and posttraining data on work intention, mindfulness, and perceived stress were collected. Age, gender, and other medication, health, and previous exercise information were collected at baseline. Surveys were delivered online by Wechat link or QR-code. It is a research design with a between-subject variable (meditation-focused group, breathing-focused group) and a within-subject variable (pre, post).

Participants

Undergraduate students (N = 120) from four yoga classes at an academically prestigious Chinese university completed a survey measuring their current work intention, mindfulness, and stress, both at the beginning and the end of one semester. There were 27–32 students in each class. Participants were invited by survey links and made decisions to participate in this study by their own. Students received course credit for their participation. Before data collection, the university's institutional review board approved the research protocol for human subjects.

Power analysis showed that the repeated ANOVA with within-between interaction needed a sample size of 90 at the power level of 0.80 (α = 0.05 with effect size of 0.15 and correlation among repeated measures of 0.50). Survey invitations were delivered to 120 participants. Individuals who have regular practice of yoga or similar techniques in the previous year were excluded (Tong et al., 2020), and there were 101 valid data for pre-survey. The final sample, with matched pre- and post-intervention measures, included 86 students (with five males) aged between 19 and 23 (M = 20.79; SD = 1.00). The attrition rate is 71.7%, and there is no significant difference on age or gender between the attrition and remained group. A total of 46 participants from two yoga classes were designated into the breathing-focused yoga group, while 40 participants from the other two yoga classes were designated into the meditation-focused yoga group. These two groups did not differ on demographic (i.e., age, gender) or pre-intervention measures (i.e., work intention, mindfulness, stress), based on t-tests analyses.

Hatha Yoga Intervention Program

Usually, one-time breathing intervention lasts for 1–20 min (Joshi and Telles, 2009; Telles et al., 2011; Saoji et al., 2018; Tellhed et al., 2019), and yoga exercise may be more effective when different parts function together. Thus, our study aimed to utilize a normal 80-min yoga session with a valid 10-min practice of meditation/breathing and compare the relative importance of meditation and breathing across 12 sessions of yoga practices. To conduct a fair comparison, the participants would be requested to breathe at a low rate similar to mediation, but breathing deeply into the abdomen, and pursue and develop awareness of in-and-out breathing (Brown and Gerbarg, 2009). Although meditation can be divided into two categories as focusing on mental processes or focusing on bodily processes (Hendriks, 2018), meditation-focused yoga practice in this study focused on the mental processes including focused attention, open monitoring, and visualization (Jindal et al., 2013).

Participants performed 80 min of Hatha yoga exercise (Riley and Park, 2015) in a morning yoga class per week for 12 weeks. Each class comprised of three main stages, including meditation or breathing (10 min, Stage 1), posture-holding exercise (60 min, Stage 2), and relaxation (10 min, Stage 3), as shown in **Table 1**. Students were directed to do meditations in the meditation-focused yoga group ("Please adjust

TABLE 1 | Hatha Yoga intervention program.

Stage (time)	Breathing-focused group	Meditation-focused group
1. Intervention (10 min)	Breathing: Participants were instructed to engage in slow and rhythmic breathing performed deeply into the abdomen and through the nostrils (Brown and Gerbarg, 2009), as indicated as initial breath regulation in Hatha yoga, focus attention on the breathing (Kabat-Zinn, 2003) and pursue and develop awareness of in-and-out breathing (Brown and Gerbarg, 2009)....“Please adjust your posture and close your eyes. . .Continue to breathe slowly and deeply. . .Observe breathing deep into your chest, into your abdomen. . .Feel the movement of diaphragm and abdomen wall and the extension of the spine. . .Visualize the breath moving up and down and in and out your body. . .Feel the temperature of our breath in and out. . .Feel the steady rhythm of smooth breathing. . .”	Mediation: Participants were instructed to engage in imagination of nice and vivid pictures in mind with voluntarily focused attention and non-reactive open monitoring of the contents of own experience (Jindal et al., 2013). “Please adjust your posture and close your eyes. . .Imagine some pictures you like. . .Gaze at the picture in details and keep focused. . .Draw back your attention when realizing you are distracted. . .Feel your inner calm state. . .”
2. Posture (60 min)	Posture-holding includes 10–12 postures after warm-up such as forward folding, bridge pose, cobra, bow, waist rotating, downward facing dog, cat stretch, warrior, triangle, tree. Practice 6–10 times for each posture. Stay in each posture for 30–60 s.	
3. Relaxation (10 min)	Relaxation means to lie in tranquil, stop any physical and mental activities, and relax each part of the body. The instructor speaks out names of specific body parts to lead the scanning relaxation. Finally, the instructor describes one or two pictures with relaxation and calm.	

your posture and close your eyes. . .Imagine some pictures you like. . .Gaze at the picture in details and keep focused. . .Draw back your attention when realizing you get distracted. . .Feel your inner calm state. . .”) while doing breathing in the breathing-focused yoga group (“Please adjust your posture and close your eyes. . .Keep breathing slowly and deeply. . .Observe your own breathing deep into your chest, into your abdomen. . .Feel the movement of diaphragm and abdomen wall and the extension of the spine. . .Visualizing the breath moving up and down and in and out your body. . .Feel the temperature of our breath in and out. . .Feel the steady rhythm of smooth breathing. . .”) during Stage 1 for each class. Participants in the meditation-focused yoga group were instructed to engage in imagination of nice and vivid pictures in mind with voluntarily focused attention and non-reactive open monitoring of the contents of own experience (Jindal et al., 2013). Participants in the breathing-focused yoga group were instructed to engage in a slow and rhythmic breathing performed deeply into the abdomen and through the nostrils (Brown and Gerbarg, 2009), indicated as initial breath regulation in Hatha yoga, focus their own attention on the breath (Kabat-Zinn, 2003), and pursue and develop awareness of in-and-out breathing (Brown and Gerbarg, 2009).

The intervention plan was strictly followed in each session. The participants had full participation and involvement in each session of the yoga practices. The attendance rate for all sessions was 100%.

The Instructor

These interventions were provided by the same instructor using the same instructions and the same music across the two conditions each week. The instructor was the first author of this paper, who designed the schema for yoga intervention. She was a female tenured professor in the department of physical education with more than 13 years of experiences teaching and coaching yoga to undergraduate students. She was a senior fitness yoga trainer certified by the Federation of University Sports of China. She also held certification in instructing Yogi Yoga, a registered yoga school by Yoga Alliance USA. Additionally, her massive open online yoga course (MOOC) achieved the national online open course certification from the National Department of Education, which is also listed in the global online course platform of Coursera and is selected by over 220,000 students.

Instrumentations

Demographic Survey

Participants were requested to fill in the blanks with their student ID and age. They were asked to choose the class they took and their gender.

Work Intention

Work intention was measured by six items in both pre- and post-training surveys. It was developed for this research according to the definition of work intention (Ajen and Fishbein, 1980). Participants were requested to rate on a seven-point scale ranging from 1 (very much unwilling) to 7 (very much willing) about their willingness to complete the survey. A sample item is phrased as “please indicate how much you want to continue completing the remaining survey right now.” The reliabilities are αs = 0.97 and 0.98 for pre- and post-interventions, respectively.

Mindfulness

Mindfulness was measured by Brown and Ryan’s (2003) 15-item Mindful Attention and Awareness Scale on a seven-point scale ranging from 1 (never) to 7 (always). Participants were requested to rate how frequently each situation occurs recently, rather than whether they generally agree. A sample item is stated as “It seems I am ‘running on automatic’ without much awareness of what I’m doing” (reverse scored). The reliabilities are αs = 0.86 and 0.91 for pre- and post-interventions, respectively.

Perceived Stress

Stress was measured by seven items adopted from the Depression Anxiety Stress Scale (Lovibond and Lovibond, 1995) on a seven-point scale ranging from 1 (never) to 7 (always). The instruction for administering this survey was the same with the mindfulness measure. It was used in previous yoga literature (Tong et al., 2020). Sample items include, “I found it difficult to relax” and “I tended to over-react to situations.” The reliabilities are αs = 0.89 and 0.90 for pre- and post-interventions, respectively.

Data Analysis

We conducted a repeated-measure multivariate analysis of covariance (MANCOVA), followed by univariate analyses, to examine the differences between meditation-focused and breathing-focused yoga interventions over the semester, in terms of ratings of work intention, mindfulness, and stress. Many previous yoga researches focused on a designated group of age and sex (such as middle-aged women, adolescence, undergraduates, see Quach et al., 2016; Philips et al., 2019). Some research explored how age or sex were related to yoga practice effect (Savita, 2006; Cahn et al., 2017; Rojiani et al., 2017) and some controlled demographic variables in empirical studies (Fishbein et al., 2016; Cahn et al., 2017; Tong et al., 2020). Moreover, age and/or sex were found to be significantly related to outcomes of work motivation (Boumans et al., 2012), mindfulness (Edwards, 2019), and stress (Folkman et al., 1987). Thus, age and gender were included as covariates[1] in this model. Pre- and post-measures were analyzed as within-group variables, and the intervention type was the between-group variable.

TABLE 2 | Descriptive statistics for each group, mean (SD).

Variable	Breathing-focused group	Meditation-focused group
Age	20.63 (1.10)	20.98 (0.83)
Gender (% women)	95.65%	92.50%
N	46	40
Pre-intervention		
Work intention	4.48 (1.49)	4.36 (1.49)
Mindfulness	4.50 (0.89)	4.50 (0.91)
Stress	3.87 (1.26)	3.73 (1.33)
Post-intervention		
Work intention	4.36 (1.59)	3.56 (1.64)
Mindfulness	4.90 (1.04)	4.45 (1.04)
Stress	3.29 (1.21)	3.74 (1.26)

TABLE 3 | Correlations between research variables.

Variable	1	2	3	4	5	6	7	8	9
1 Intervention group	–								
2 Pre-work intention	−0.04	–							
3 Pre-mindfulness	0.001	0.15	–						
4 Pre-stress perception	−0.06	0.03	−0.56**	–					
5 Post-work intention	−0.24*	0.56**	0.15	0.02	–				
6 Post-mindfulness	−0.21*	0.07	0.59**	−0.32**	0.32**	–			
7 Post-stress perception	0.18	0.05	−0.42**	0.36**	−0.24*	−0.72**	–		
8 Age	0.17	0.02	−0.15	0.03	−0.01	−0.07	−0.04	–	
9 Sex	0.07	−0.29**	−0.03	0.01	−0.17	−0.06	0.06	−0.30**	–

*N = 86. *p < 0.05, **p < 0.01.*

RESULTS

Table 2 presents the descriptive statistical results for all research variables over time for each intervention group, and **Table 3** presents the correlation matrix. The intra-class correlations (ICCs) for all focal variables were small (ranging 0.01–0.03), indicating that there was none to minimal clustering effect and that the data observations for these focal constructs were independent despite class memberships.

The test of homogeneity of covariance matrices was not significant [Box's M = 25.81, $F_{(21,\ 24883)}$ = 1.13, p = 0.30], indicating that the observed covariance matrices of the dependent variables were equal across groups. Results from the pre-post training MANCOVA revealed significant group differences with a median effect size [Wilks' lambda, Λ = 0.90, F(3, 80) = 3.10, p = 0.031, η^2 = 0.104]. Subsequently, significant group by time interaction effects were observed for work intention [$F_{(1,\ 82)}$ = 5.22, p = 0.025, η^2_p = 0.060), mindfulness [$F_{(1,\ 82)}$ = 6.33, p = 0.014, η^2_p = 0.072], and stress [$F_{(1,\ 82)}$ = 4.20, p = 0.044, η^2_p = 0.049], respectively. To characterize the meaning of these interactions, marginal means of the models were estimated for each group at pre and post measures, as shown in **Figures 1–3**. Simple effect analyses showed that between-group differences emerged at post-intervention for work intention [t(84) = 2.30, p = 0.024], mindfulness [t(84) = 2.00, p = 0.049], and stress [t(84) = −1.68, p = 0.096]. Students in the breathing-focused group had significant higher work intentions and mindfulness but marginally lower stress than students in the meditation-focused group. Examination of the change for each intervention group also supported the function of breathing-focused yoga intervention. Comparatively, the breathing-focused group had significant increase in mindfulness ($B_{breathing}$ = 0.42 ± 0.13, p = 0.002; $B_{meditation}$ = −0.07 ± 0.14, p = 0.64) and decrease in stress ($B_{breathing}$ = −0.61 ± 0.21, p = 0.005; $B_{meditation}$ = 0.04 ± 0.23, p = 0.87) over the semester. The meditation-focused group significantly decreased work intention ($B_{breathing}$ = −0.09 ± 0.22, p = 0.66; $B_{meditation}$ = −0.83 ± 0.23, p = 0.001).

DISCUSSION

The aim of this research was to compare the relative importance of meditation-focused and breathing-focused yoga practice in energy retention and related stress reduction in a group of undergraduate students. Major findings are: (1) Students in the breathing-focused yoga group reported significant increase in mindfulness and significant decrease in stress, while students in the meditation-focused yoga group reported significant decrease in work intention; (2) Students in the breathing-focused yoga

[1] Since there were no age and gender differences between groups in this research, we also analyzed the data without any controls. Without controlling for age and gender, the MANOVA and ANOVAs results are very similar. Results from the pre-post training MANOVA revealed significant group differences with a median effect size (Wilks' lambda, Λ = 0.91, F(3.82) = 2.81, p = 0.045, η^2 = 0.093). Subsequently, group by time interaction effects were observed significant for work intention ($F_{1,84}$= 4.74, p = 0.032, η^2_p = 0.053), mindfulness ($F_{1,84}$ = 5.72, p = 0.019, η^2_p = 0.064), and marginally for stress ($F_{1,84}$ = 3.81, p = 0.054, η^2_p = 0.043), respectively.

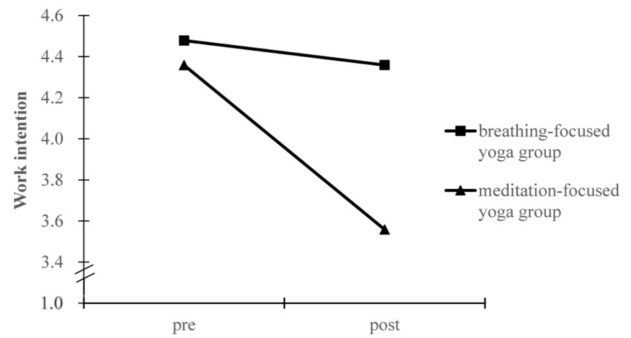

FIGURE 1 | Marginal means estimated for work intention before and after intervention by group.

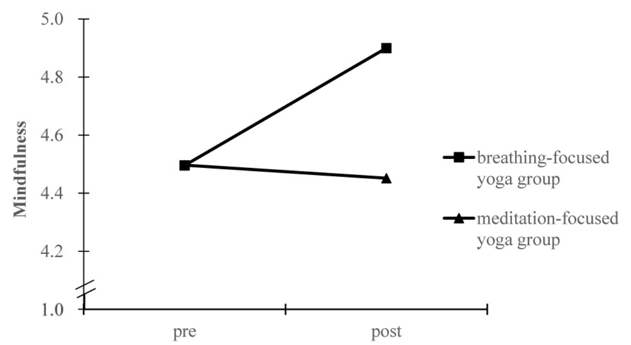

FIGURE 2 | Marginal means estimated for mindfulness before and after intervention by group.

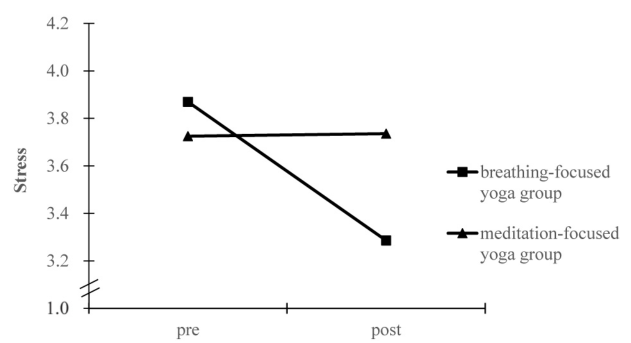

FIGURE 3 | Marginal means estimated for stress before and after intervention by group.

group had significant higher work intentions and mindfulness and had marginally less stress than students in the meditation-focused yoga group at post-intervention.

It was found that students in the meditation-focused yoga group reported significant decrease in work intention, while the breathing-focused group did not have any significant changes in terms of work intention. It may be due to the time for the post-training survey was in the end of a normal semester, and students were busy coping with the final exams. With much resources invested into the final exams, students may have limited energy to spend in other tasks such as filling out a survey. It can be indicated as lower levels of purposeful action (Ajen and Fishbein, 1980).

We found that breathing-focused yoga practice is more effective than meditation-focused yoga practice in increasing mindfulness and reducing stress. It is different from previous no-difference findings (Wheeler et al., 2019). As discussed in the Introduction section, a 20-min intervention without a full yoga intervention (combined with postures) and without an intervention of multiple sessions may limit the function of breathing and meditation (Wheeler et al., 2019). Our findings are consistent with previous literature supporting that breathing directly increase oxygenation to strengthen the physical body (Brown and Gerbarg, 2005) and achieves energy and resources (Joshi and Telles, 2009; Telles et al., 2011; Zaccaro et al., 2018), while meditation achieves serenity and relaxation (Koopmann-Holm et al., 2013; Jones et al., 2018; Philips et al., 2019). When people more easily achieve energy and resources through breathing-focused yoga practice, they would not frequently feel stressed, compared to meditation-focused practice. Moreover, breathing may be more practical and is related to vigor and alertness (Zaccaro et al., 2018), while meditation may be not easily learned and practiced for undergraduates (Brown and Gerbarg, 2009). Thus, breathing may easily help undergraduates achieve better attention and awareness (i.e., mindfulness), which also leads to lower stress. Although our findings may be due to the relatively easily achieved benefits of yoga breathing and biological energy enhancement by better oxygenation, it may be also due to the difference between awareness of inner body and outer imagination. When people are inexperienced yoga practitioners, practice of mental attention on inner body may be easier to heighten the level of spiritual awareness than through outer imagination. However, all the mentioned benefits of mediation (Hendriks, 2018) may be achieved when people are experienced.

The present research contributes to the yoga literature by going further in disclosure the nature of important yoga components. It provided evidence showing the advantage of breathing-focused yoga over meditation-focused yoga practice in terms of energy retention, attention and awareness, and stress reduction, which confirms the value to direct a nuanced examination of separate yoga components. This stream of research would indicate the relative importance of yoga components and disclose the nature of these components. Practically, our findings would help novices find a quick and easy way to achieve benefits of yoga, as breathing is easier than meditation (Brown and Gerbarg, 2009). Practitioners can take into separate yoga components into detailed consideration when designing a new yoga program. For example, postures with more breathing and less meditation may be an effective yoga program for young and inexperienced people.

Besides the above strengths, there are some limitations. First, all the indicators were self-reported. The benefits of yoga components may be subjective rather than objective. Future research may use other ratings or biological indicators such as cortisol and event-related potentials (P300) to better support the function of individual yoga components. Since breathing regulation involves both biological techniques and mental awareness (Ramdev, 2005) and meditation involves both mental and bodily processes (Hendriks, 2018), the biological indicators may also help to examine detailed components of breathing and meditation. Second, meditation may be better conducted in older adults such as the working population with richer personal experience than undergraduate students. Future research needs to explore whether our findings can be generalized into other groups.

Another limitation of the study is with the measurement of work intention. Work intention is an indication of energy, which was hypothesized to be an important psychological benefit of yoga practice, especially of breathing-focused yoga practice. The measure showed sound internal consistency reliability in this current study. However, asking the participants to reference to an immediate cognitive task (i.e., completing the survey) as representation of work may not thoroughly capture undergraduate students' work or occupation in general, although completing the survey was the immediate task they were asked to perform. Future research may examine whether yoga would energize undergraduate students' work intention in other tasks (e.g., studying in a course, working for a part-time job, cramming for an exam).

Finally, lack of quality of delivery data should be recognized as an area of weakness for fidelity check in this study. Future research is encouraged to collect data about participants' effort and attentions.

CONCLUSION

Yoga breathing is an important component and can achieve better benefits than yoga mediation in undergraduate students. Designing a yoga program with combination of breathing and postures facilitates psychological resources and stress coping.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Committee for Protecting Human and Animal Subjects, School of Psychological and Cognitive Sciences, Peking University. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

XQ, JT, ZH, and SC contributed to conception and design of the study. XQ conducted the experiment. JT, XZ, and SC analyzed the data. JT wrote the first draft of the manuscript. All authors contributed to manuscript revision and 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/fpsyg.2020.560152/full#supplementary-material

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Acupuncture for Improving Cognitive Impairment After Stroke: A Meta-Analysis of Randomized Controlled Trials

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Objective: This meta-analysis evaluated the efficacy of acupuncture in improving cognitive impairment of post-stroke patients.

Design: Randomized controlled trials (RCTs) investigating the effects of acupuncture compared with no treatment or sham acupuncture on post-stroke cognitive impairment (PSCI) before December 2019 were identified from databases (PubMed, EMBASE, Ovid library, Cochrane Library, Chinese National Knowledge Infrastructure, VIP Chinese Periodical Database, Wanfang Database, and SinoMed). The literature searching and data extracting were independently performed by two investigators. Study quality was assessed using the Cochrane Handbook for Systematic Reviews of Interventions. Meta-analyses were performed for the eligible RCTs with Revman 5.3 software.

Results: Thirty-seven RCTs (2,869 patients) were included in this meta-analysis. Merged Random-effects estimates of the gain of MMSE (Mini-Mental State Examination) or MoCA (Montreal Cognitive Assessment) were calculated for the comparison of acupuncture with no acupuncture or sham acupuncture. Following 2–8 weeks of intervention with acupuncture, pooled results demonstrated significant effects of acupuncture in improving PSCI assessed by MMSE (MD [95% CI] = 2.88 [2.09, 3.66], $p < 0.00001$) or MoCA (MD [95% CI] = 2.66 [1.95, 3.37], $p < 0.00001$).

Conclusion: The results suggest that acupuncture was effective in improving PSCI and supported the needs of more rigorous design with large-scale randomized clinical trials to determine its therapeutic benefits.

Keywords: MMSE, cognitive impairment, electroacupuncture, acupuncture, post stroke

INTRODUCTION

Stroke is a disease that causes high rates of mortality and disability worldwide (Wu et al., 2010). Cognitive impairment is a frequent condition after stroke (Tatemichi et al., 1994; Patel et al., 2003), and its prevalence ranges from 17 to 92% (Pasi et al., 2012). Cognitive rehabilitation could enhance the quality of life for post-stroke patients, which included a comprehensive cognitive improvement program treating cognitive dysfunction involving disorientation, sensory disorders, attention disorders, executive function disorders, and memory disorders (Berrol, 1990; Choi and Twamley, 2013). The clinical depression is characterized by behavioral, cognitive, and emotional features (Merriman et al., 2019). Cognitive performance is associated with symptoms of depression (Nakling et al., 2017), and early cognitive impairment after stroke predicts long-term depressive symptoms in patients (Nys et al., 2006).

Acupuncture therapy has been used widely to promote motor recovery after stroke (Hu et al., 1993; Lee et al., 2003). Because of its low cost with low adverse events, acupuncture has also been used to improve the cognitive function of stroke patients, mostly in China, and it is receiving increasing attention among western countries (Johansson et al., 1993; NIH consensus conference, 1998). A considerable number of clinical trials showed the potential role of acupuncture as a promising treatment for post-stroke cognition impairment, but some trials suggest that acupuncture does not affect post-stroke cognitive impairment (PSCI) (Guo et al., 2007). The conflicting results may be caused by a small sample size of the trials and a flaw of study design.

Two systematic reviews (Liu et al., 2014; Wang, 2017) were performed; however, the studies were limited by small sample size. Liu et al. (2014) reported the meta-analysis results of 21 trials from 2006 to 2012; however, those trials had 12 different methods to evaluate cognitive function. Therefore, the largest dataset had only 116 patients from four studies [with Mini-Mental State Examination (MMSE) as the outcome measure]. In Wang's systematic review, only 15 studies with 1,085 subjects from 2008 to 2016 were included.

Since the last systematic review, many more clinical trials of acupuncture for post-stroke impairment were conducted; however, all of these clinical trials were limited by a small sample size or inconsistent selection criteria for the assessment of cognitive function. Therefore, with the further increased randomized controlled trials (RCT) evidence, there is a strong need to perform a systematic review to evaluate the therapeutic effect of acupuncture to treat PSCI.

In this study, we hypothesize that acupuncture is effective to improve cognitive function after stroke as compared to sham or no acupuncture. This systematic review and meta-analysis aimed to validate the efficacy of acupuncture in treatment for PSCI with MMSE or Montreal Cognitive Assessment (MoCA), which are the most generally used assessment tools for cognitive impairment (Foreman et al., 1996; Nasreddine et al., 2005).

MATERIALS AND METHODS

Inclusion Criteria and Exclusion Criteria

The inclusion criteria were the following: (1) type of studies: only randomized controlled trials (RCTs) of acupuncture for PSCI in English or Chinese language which were published before December 2019 were included; (2) type of participants: post-stroke patients (over 18 years old) with PSCI were included without restriction on gender, race, or nation; (3) type of interventions: the RCTs that used traditional acupuncture or electroacupuncture to treat PSCI were included; (4) outcome measurements: the outcome was assessed by MMSE or MoCA; and (5) type of comparators: the comparative interventions could be sham acupuncture or conventional treatment with rehabilitation. A RCT was included if acupuncture was used at acupoints as the sole treatment or as an adjunct to other treatments for cognition impairment after stroke. If studies included three or over three groups with only one group receiving acupuncture, and there is a control group without receiving acupuncture treated consistent with the acupuncture group, the data of acupuncture group, and control group were chosen for this study. If studies included three or over three groups with two or over two groups receiving acupuncture, a routine acupuncture group was chosen as the experiment group, and the group not receiving any acupuncture treated consistent with the acupuncture group was chosen as a control group.

The exclusion criteria were the following: (1) cognition impairment caused by other diseases except for stroke; (2) studies without a control group (control group treated consistent with the acupuncture group except receiving acupuncture); (3) studies compared different types of acupuncture; (4) studies compared the effect of acupuncture with a drug; (5) studies adopted complex treatment without specifying the sole effects of acupuncture; (6) cognition outcome measured by another assessing system except for MMSE or MoCA; (7) studies without standardized indices of curative effect or detailed results of treatment will be excluded; and (8) full texts cannot be obtained or the data cannot be extracted.

Identification of Eligible Trials

For search strategy, we searched articles published before December 2019 in the following databases: Chinese Science and Technology Periodical Database (VIP), China National Knowledge Infrastructure (CNKI), Wan Fang Database, PubMed, Embase, Web of Science, and the Ovid Library, and using the combining medical subject headings and keyword terms for stroke, acupuncture, and cognition. The search terms included "acupuncture/electroacupuncture" AND "stroke/stroke rehabilitation/cerebrovascular accident/brain ischemia/cerebral hemorrhage/CVA/cerebral embolism" AND "cognition/cognitive." At the same time, some studies were extracted from the references in the full-text articles. Articles were restricted to English and Chinese languages.

Assessment of Risk of Bias

The methodological quality and the risk of bias of the included studies were compiled using the risk of bias tool in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.3) by two reviewers (L.Z. and Y.W.) independently. This instrument included seven specific domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

Data Extraction

Studies were screened by two investigators independently. Disagreements were settled by consensus or a third investigator. The extracted data included general characteristics (author and year of publication), patient characteristics (sample size, mean age, and disease type), intervention characteristics (type and duration), and main outcomes and adverse events. When a given study reported the outcome with more than one cognitive function assessment, we gave preference primarily to MMSE or MoCA.

Statistical Analysis

All statistical analyses were performed with Revman 5.3 software (The Cochrane Collaboration software unpdate). Since the outcomes in studies were continuous variables, the mean differences (MDs) with 95% confidence intervals (CIs) were calculated. Heterogeneity was showed by I^2 index values with a p-value and percentage, respectively. A fixed-effects model would be used in a meta-analysis when heterogeneity was adopted ($I^2 <$ 25% or 50% $> I^2 \geq$ 25% with $p > 0.1$). Otherwise ($I^2 \geq$ 50% or 50% $> I^2 \geq$ 25% with $p \leq 0.1$) the random-effects model would be used.

The stability of the results was confirmed by sensitivity analysis. Publication bias was assessed by Begg's test with STATA software (version 12.0, Stata Corp). Quality of evidence was assessed with GRADEpro in website (www.gradepro.org).

RESULTS

Eligible Studies

The workflow of literature screening and inclusion is shown in **Figure 1**. The initial literature search yielded 977 studies. Out of 977 studies, 72 studies were duplicated. A total of 905 studies were assessed for eligibility by titles and abstracts screening. There were 69 papers that compared the effect of acupuncture in patients with PSCI. With full-text reading, 32 articles were excluded, and 37 studies were included in the synthesis. The 37 studies are 31 journal articles (Huang et al., 2008; Li and Zhang, 2008; Lin et al., 2010; Jia and Meng, 2011; Sun and Wu, 2011; Bai et al., 2012; Li et al., 2012, 2019; Liu and Feng, 2013; Song et al., 2013; Wang, 2014, 2019; Wang et al., 2014, 2019; Yang, 2014; Liu et al., 2015a,b; Zeng et al., 2015; Cai et al., 2016; Shao, 2016; Liu, 2017; Wang H. et al., 2017; Wang Z. et al., 2017; Zhang et al., 2017; Du et al., 2018; Jia and Lv, 2018; Ma et al., 2018; Wang and Li, 2018; Shi and Wei, 2019; Zhou H. et al., 2019; Zhou J. et al., 2019) and 6 dissertations (Jiang, 2011; Kang, 2011; Yang, 2011; Feng, 2013; Lu, 2014; Sun, 2017), which involved 2,869 patients (1,442 patients in the treatment group and 1,427 patients in the control group) in total. All those studies were conducted in China. Thirty-six papers were published in the Chinese language. **Table 1** shows the detailed information on the characteristics of the included studies. The ages of the patients range from 35 to 80 years. Seven trials did not describe the sex of the patients, while other trials included more male than female participants. The treatment period ranged from 2 to 12 weeks; the frequency of the sessions ranged from two sessions per day to five sessions per week. The chronicity of stroke ranged from 3 to 1,080 days, but most of those patients were treated within 6 months of onset. Twenty-three trials were conducted by manual acupuncture stimulation, and the other 14 trials used electroacupuncture only. The cognitive function assessment of all included studies was MMSE or MoCA.

Assessment of Risk of Bias

All RCTs had a low risk of bias (ROB) about adequate sequence generation. Eight RCTs had a low ROB with allocation concealment, while 9 RCTs had a high ROB, and 20 had an unclear ROB. Concerning participant blinding, one RCT had low ROB and the others had a high or unclear ROB. About assessor blinding, only three RCTs had a low ROB.

All 37 RCTs had a low ROB in incomplete outcome data addressed and selective outcome reporting. Thirty-four RCTs had an unclear ROB in other sources of bias. The results of the ROB assessment are shown in **Table 2**, **Figure 2**.

Meta-Analysis of the Results

The pooled meta-analysis of the data showed a weighted mean difference of 2.88 and 95% confidence intervals (CI) of 2.09–3.66 on the MMES ($p < 0.001$, $n = 2{,}349$; **Figure 3**).

Subgroup analyses showed weighted mean differences of 2.52 (95% CI: 1.86–3.18, $n = 1{,}622$) and 3.45 (95% CI: 2.09–3.66, $n = 727$) for acupuncture subgroup and electropuncture subgroup, respectively.

The pooled meta-analysis of the data showed a weighted mean difference of 2.66 and 95% confidence intervals of 1.95–3.37 on the MoCA ($p < 0.001$, $n = 1{,}129$; **Figure 4**).

Subgroup analyses showed weighted mean differences of 2.55 (95% CI: 1.71–3.39, $n = 652$) and 2.81 (95% CI: 1.42–4.02, $n = 477$) for acupuncture subgroup and electropuncture subgroup, respectively.

The results indicated that acupuncture had a significant effect on PSCI, and no adverse events were reported in those studies.

Sensitivity Analysis, Publication Bias, and Overall Quality of Evidence

High heterogeneity was shown in results ($I^2 = 93$ and 55 for MMSE and MoCA, respectively), so subgroup analyses were done based on different methods of acupuncture between manual acupuncture (acupuncture) and electropuncture. The results of subgroup analyses showed that intra-group heterogeneity remained high in subgroups ($I^2 > 50$), and the inter-group heterogeneity between subgroups was not too much ($I^2 <$ 50). Then sensitivity analysis was conducted by excluding the maximum weight studies in outcomes on subgroup analyses. The results showed that there was little influence on the pooled MD value. Then a study was removed at a time and the others analyzed to assess whether the results could have been influenced significantly by a single study. The results also showed no apparent fluctuation. These analyses confirmed the stability of the results of pooled MD value. Begg's tests showed no significant publication bias with symmetrical funnel plots. The overall quality of evidence was rated as moderate for MMSE and MoCA (**Figure 5**).

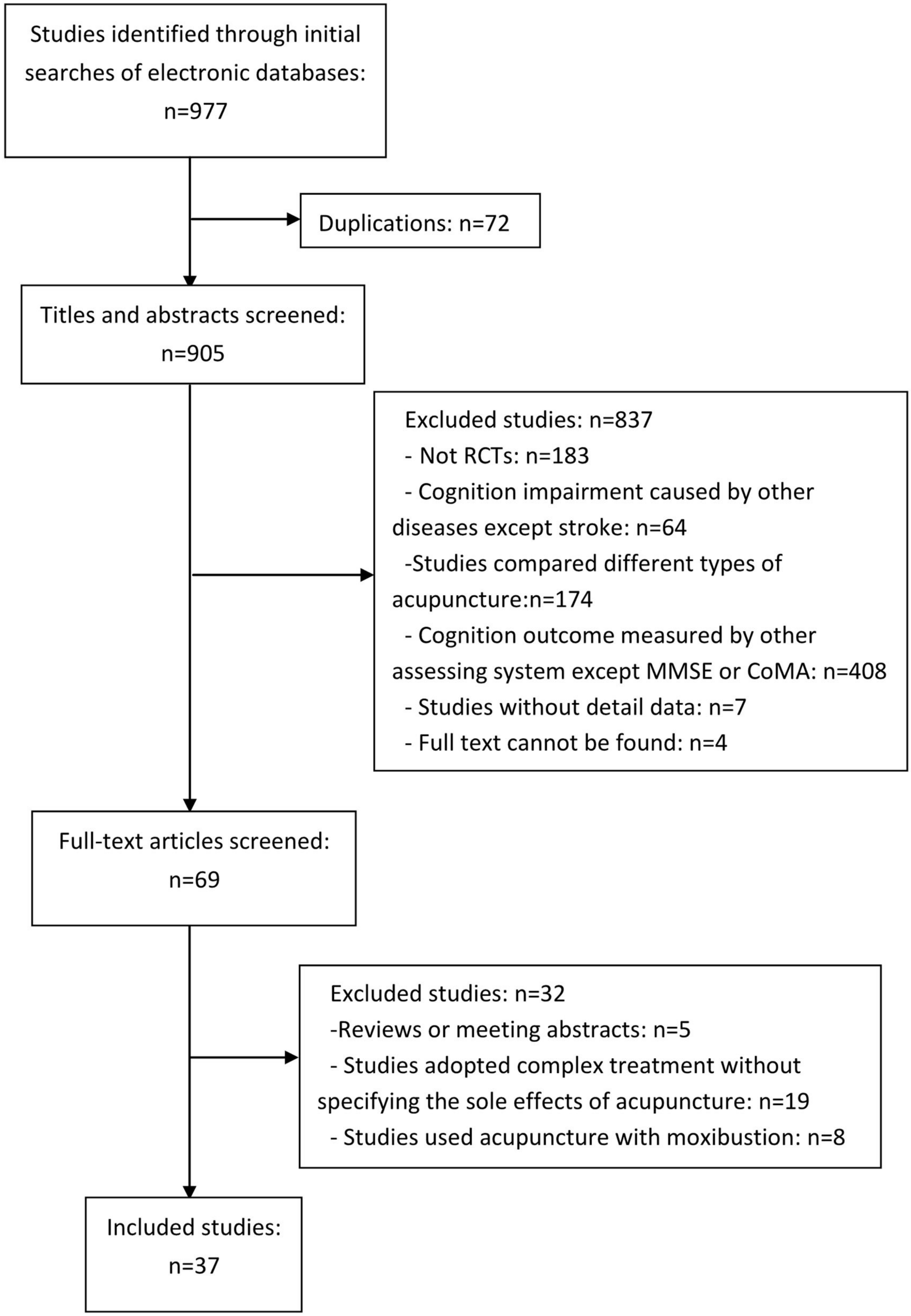

FIGURE 1 | Literature screening flow diagram.

TABLE 1 | Characteristics of included studies.

References	Patients no.		Ages (years)		Type of stroke	Outcome measures (MMSE/MoCA)	Therapy duration (wk)	Intervation		Source of diagnostic criteria for cerebral vascular diseases	Source of diagnostic criteria for PSCI
	Treatment	Control	Treatment	Control				Treatment	Control		
Sun (2017)	30	28	60.63 ± 8.273	61.29 ± 7.693	Ischemic stroke or hemorrhage	MMSE and MoCA	6	Acupuncture+ control treatment	Conventional treatment + rehabilitation	FNACCVD confirmed by head CT or MRI	DSM-IV
Shao (2016)	28	28	63 ± 5		Ischemic stroke or hemorrhage	MMSE	12	Acupuncture+ control treatment	Conventional treatment + rehabilitation	CECS, Chinese expert consensus standards	DSM-IV
Liu et al. (2015a)	32	30	51.97 ± 9.11	51.30 ± 10.57	Ischemic stroke or hemorrhage	MoCA	4	Electropuncture+ control treatment	Conventional treatment + rehabilitation	CECS, Chinese expert consensus standards	MoCA
Cai et al. (2016)	52	49	57.75 ± 13.74	56.18 ± 11.86	Ischemic stroke or hemorrhage	MMSE and MoCA	12	Acupuncture+ control treatment	Conventional treatment + rehabilitation	CECS, Chinese expert consensus standards	MMSE
Zeng et al. (2015)	50	50	66 ± 12	68 ± 10	Ischemic stroke or hemorrhage	MoCA	4/8	Electropuncture+ control treatment	Conventional treatment + rehabilitation	FNACCVD confirmed by head CT or MRI	MoCA
Wang (2014)	33	31	66.4 ± 3.0		Ischemic stroke or hemorrhage	MMSE	3	Acupuncture+ control treatment	Conventional treatment + xingnaojing	FNACCVD confirmed by head CT or MRI	Not shown
Lu (2014)	30	30	63.27 ± 11.88	63.90 ± 8.48	Ischemic stroke or hemorrhage	MoCA	4	Acupuncture+ control treatment	Conventional treatment + rehabilitation	CECS, Chinese expert consensus standards	MoCA
Zhai (2012)	55	55	59.2		Ischemic stroke	MMSE	12	Acupuncture+ control treatment	Conventional treatment + rehabilitation	FNACCVD confirmed by head CT or MRI	Not shown
Bai et al. (2012)	30	30	60 ± 6	60 ± 6	Ischemic stroke or hemorrhage	MMSE	4	Acupuncture+ control treatment	Conventional treatment + piracetam	FNACCVD confirmed by head CT or MRI	CCSE
Li et al. (2012)	48	46	68.29 ± 8.22	69.22 ± 7.88	Ischemic stroke or hemorrhage	MMSE	12	Acupuncture+ control treatment	Conventional treatment + nimodipine	FNACCVD confirmed by head CT or MRI	MMSE
Yang (2011)	20	20	59.00 ± 8.46	59.30 ± 8.42	Ischemic stroke or hemorrhage	MMSE	8	Acupuncture+ control treatment	Conventional treatment + rehabilitation	FNACCVD confirmed by head CT or MRI	MMSE
Sun and Wu (2011)	36	36	63.6 ± 5.8	64.1 ± 5.5	Ischemic stroke	MMSE	4	Acupuncture+ control treatment	Conventional treatment + aricept	FNACCVD confirmed by head CT or MRI	MMSE
Kang (2011)	24	24	60.67 ± 6.93	62.71 ± 5.34	Ischemic stroke or hemorrhage	MMSE	8	Electropuncture+ control treatment	Conventional treatment + rehabilitation	FNACCVD confirmed by head CT or MRI	MMSE
Jiang (2011)	20	20	62.85 ± 5.67	61.75 ± 6.35	Ischemic stroke or hemorrhage	MMSE	8	Electropuncture+ control treatment	Conventional treatment + rehabilitation	FNACCVD confirmed by head CT or MRI	CCSE

(Continued)

TABLE 1 | Continued

References	Patients no.		Ages (years)		Type of stroke	Outcome measures (MMSE/MoCA)	Therapy duration (wk)	Intervation		Source of diagnostic criteria for cerebral vascular diseases	Source of diagnostic criteria for PSCI
	Treatment	Control	Treatment	Control				Treatment	Control		
Jia and Meng (2011)	50	50	65 ± 2	58 ± 3	Ischemic stroke	MoCA	12	Acupuncture+ control treatment	Conventional treatment + rehabilitation + nimodipine	CECS, Chinese expert consensus standards	Diagnosis criteria shown in reference (Jia, 2004)
Lin et al. (2010)	30	30	63 ± 17	56 ± 13	Ischemic stroke	MMSE	3	Acupuncture+ control treatment	Conventional treatment + xingnaojing	FNACCVD confirmed by head CT or MRI	MMSE
Huang et al. (2008)	40	40	59.22 ± 10.6	61.05 ± 9.68	Ischemic stroke	MMSE	4	Acupuncture+ control treatment	Conventional treatment + xingnaojing	FNACCVD confirmed by head CT or MRI	CECVCI
Shi and Wei (2019)	55	55	60.31 ± 2.73	60.24 ± 2.65	Stroke	MMSE	4	Acupuncture+ control treatment	Conventional treatment + rehabilitation	Not shown	Not shown
Zhou J. et al. (2019)	60	60	61.44 ± 8.77	62.04 ± 8.69	Ischemic stroke or hemorrhage	MMSE and MoCA	4	Electropuncture+ control treatment	Conventional treatment + rehabilitation	CECS, Chinese expert consensus standards	DSM
Feng (2013)	40	40	51.65 ± 12.47	52.13 ± 12.77	Ischemic stroke or hemorrhage	MMSE and MoCA	4	Electropuncture+ control treatment	Conventional treatment + rehabilitation	FNACCVD confirmed by head CT or MRI	DSM-IV
Wang et al. (2019)	59	59	68.88 ± 3.64	67.71 ± 3.02	Ischemic stroke	MMSE	4	Acupuncture+ control treatment	Conventional treatment + Atorvastatin	FNACCVD confirmed by head CT or MRI	There are symptoms such as memory loss
Li et al. (2019)	40	40	66.9 ± 5.9	67.4 ± 6.1	Ischemic stroke or hemorrhage	MMSE and MoCA	6/12	Acupuncture+ control treatment	Conventional treatment+ Donepezil	FNACCVD confirmed by head CT or MRI	DSM-IV-R
Zhang et al. (2017)	42	42	62.28 ± 10.68	63.07 ± 10.59	Stroke	MMSE	4	Acupuncture+ control treatment	Conventional treatment + rehabilitation + Atorvastatin	FNACCVD confirmed by head CT or MRI	There are symptoms such as memory loss
Wang H. et al. (2017)	30	30	53.27 ± 11.62	56.73 ± 9.31	Ischemic stroke or hemorrhage	MMSE	8	Electropuncture+ control treatment	Conventional treatment + rehabilitation	FNACCVD confirmed by head CT or MRI	DSM-IV
Zhou H. et al. (2019)	40	40	61.5 ± 5.7	61.5 ± 4.4	Ischemic stroke	MMSE and MoCA	6	Electropuncture+ control treatment	Conventional treatment + rehabilitation + Perindopril	FNACCVD confirmed by head CT or MRI	Not shown
Wang Z. et al. (2017)	30	30	61.13 ± 11.42	60.06 ± 11.17	Ischemic stroke or hemorrhage	MMSE and MoCA	8	Acupuncture+ control treatment	Conventional treatment + rehabilitation	FNACCVD confirmed by head CT or MRI	DSM-IV-R

(Continued)

TABLE 1 | Continued

References	Patients no.		Ages (years)		Type of stroke	Outcome measures (MMSE/MoCA)	Therapy duration (wk)	Intervation		Source of diagnostic criteria for cerebral vascular diseases	Source of diagnostic criteria for PSCI
	Treatment	Control	Treatment	Control				Treatment	Control		
Wang et al. (2019)	78	78	69.04 ± 3.48	68.92 ± 3.65	stroke	MMSE	4	acupuncture+ control treatment	Conventional treatment + Tongluofuzheng decoction	Not shown	Not shown
Wang and Li (2018)	64	64	71.42 ± 8.67	69.33 ± 7.56	Ischemic stroke	MMSE and MoCA	6/10	Acupuncture+ control treatment	Conventional treatment + rehabilitation + nimodipine	CECS, Chinese expert consensus standards	Diagnosis criteria shown in reference (Zhang and Wang, 2004)
Yang (2014)	40	40	61.7 ± 4.8		Stroke	MMSE	3	Acupuncture+ control treatment	Conventional treatment + xingnaojing	FNACCVD confirmed by head CT or MRI	Not shown
Ma et al. (2018)	30	30	60.97 ± 7.15	60.17 ± 6.56	Ischemic stroke or hemorrhage	MMSE	2/4	Electropuncture+ control treatment	Conventional treatment + Oxiracetam + hyperbaric oxygen therapy	FNACCVD confirmed by head CT or MRI	MMSE
Jia and Lv (2018)	40	39	58.33 ± 11.13	57.45 ± 12.37	Ischemic stroke or hemorrhage	MMSE	4	Acupuncture+ control treatment	Conventional treatment + Huoxuetongluo decoction	FNACCVD confirmed by head CT or MRI	CCSE
Liu (2017)	32	32	56.9 ± 10.3	56.4 ± 10.1	Ischemic stroke or hemorrhage	MMSE	2	Electropuncture+ control treatment	Conventional treatment + rehabilitation	FNACCVD confirmed by head CT or MRI	Not shown
Liu et al. (2015b)	19	16	52.42 ± 7.62	51.06 ± 11.62	Ischemic stroke or hemorrhage	MMSE and MoCA	4	Electropuncture+ control treatment	Conventional treatment + rehabilitation	CECS, Chinese expert consensus standards	MMSE
Sun et al. (2013)	60	60	62.50 ± 4.52	63.01 ± 4.67	Ischemic stroke	MMSE	4	Electropuncture+ control treatment	Conventional treatment + rehabilitation + nimodipine	FNACCVD confirmed by head CT or MRI	MMSE
Liu and Feng (2013)	25	25	53.40 ± 8.48		Ischemic stroke or hemorrhage	MMSE	4	Electropuncture+ control treatment	Conventional treatment + rehabilitation	FNACCVD confirmed by head CT or MRI	DSM-IV-R
Wang et al. (2014)	30	30	45∼80		Ischemic stroke	MoCA	12	Acupuncture+ control treatment	Conventional treatment + nimodipine	FNACCVD confirmed by head CT or MRI	Not shown
Li and Zhang (2008)	20	20	58∼76		Ischemic stroke	MMSE	4	Electropuncture+ control treatment	Conventional treatment + rehabilitation	FNACCVD confirmed by head CT	Not shown

MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; FNACCVD, Fourth National Academic Conference of Cerebral Vascular Diseases; CT, computed tomography; MRI, magnetic resonance imaging; DSM-IV,Diagnostic and Statistical Manual of Mental Disorders(the fourth edition); DSM-IV-R, DSM-IV-Revised edition; CECS, Chinese expert consensus standards, proposed in 2005 for the prevention and treatment of cognitive dysfunction; CCSE, Cognitive Capacity Screening Examination; CECVCI, Chinese Expert consensus on vascular cognitive impairment 2007.

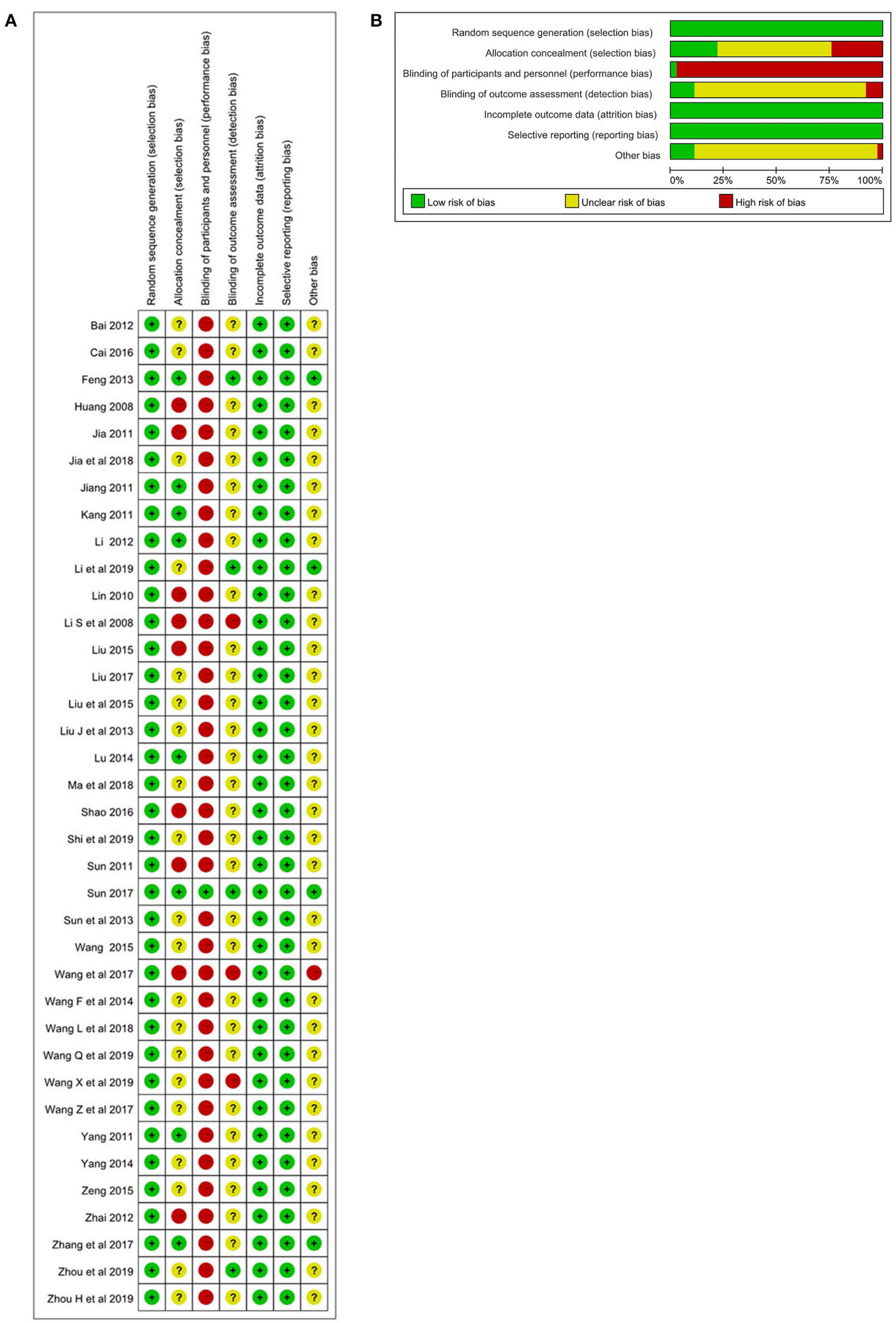

FIGURE 2 | (A) Assessment of risk of bias with selected studies. **(B)**. Risk of bias graph and summary.

TABLE 2 | Quality assessment of studies.

References	Adequate sequence generation	Allocation concealment	Blinding of participation and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective outcome reporting avoided	Other sources of bias
Sun (2017)	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Shao (2016)	Yes	No	No	Unclear	Yes	Yes	Unclear
Liu et al. (2015a)	Yes	No	No	Unclear	Yes	Yes	Unclear
Cai et al. (2016)	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
Zeng et al. (2015)	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
Wang (2014)	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
Lu (2014)	Yes	Yes	No	Unclear	Yes	Yes	Unclear
Zhai (2012)	Yes	No	No	Unclear	Yes	Yes	Unclear
Bai et al. (2012)	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
Li et al. (2012)	Yes	Yes	No	Unclear	Yes	Yes	Unclear
Yang (2011)	Yes	Yes	No	Unclear	Yes	Yes	Unclear
Sun and Wu (2011)	Yes	No	No	Unclear	Yes	Yes	Unclear
Kang (2011)	Yes	Yes	No	Unclear	Yes	Yes	Unclear
Jiang (2011)	Yes	Yes	No	Unclear	Yes	Yes	Unclear
Jia and Meng (2011)	Yes	No	No	Unclear	Yes	Yes	Unclear
Lin et al. (2010)	Yes	No	No	Unclear	Yes	Yes	Unclear
Huang et al. (2008)	Yes	No	No	Unclear	Yes	Yes	Unclear
Shi and Wei (2019)	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
Zhou J. et al. (2019)	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
Feng (2013)	Yes	Yes	No	Yes	Yes	Yes	No
Wang et al. (2019)	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
Li et al. (2019)	Yes	Unclear	No	Yes	Yes	Yes	No
Zhang et al. (2017)	Yes	Yes	No	Unclear	Yes	Yes	No
Wang H. et al. (2017)	Yes	No	No	No	Yes	Yes	Unclear
Zhou H. et al. (2019)	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
Wang Z. et al. (2017)	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
Wang et al. (2019)	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
Wang and Li (2018)	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
Yang (2014)	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
Ma et al. (2018)	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
Jia and Lv (2018)	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
Liu (2017)	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
Liu et al. (2015b)	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
Sun et al. (2013)	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
Liu and Feng (2013)	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
Wang et al. (2014)	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
Li and Zhang (2008)	Yes	No	No	No	Yes	Yes	Unclear

DISCUSSION

Our findings showed that acupuncture or electroacupuncture therapy is effective in improving the cognitive impairment of post-stroke patients by assessing with MMSE and MoCA. The gain of the mean difference is 2.88 for MMSE (CI [2.09, 3.66]), which is significant in clinical treatment (Andrews et al., 2019). The gain of the mean difference is 2.66 for MoCA (CI [1.95, 3.37]), which is also significant in clinical treatment (Wong et al., 2017).

In this study, patients in the control group were treated with conventional treatment in all 37 trials, patients had

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 acupuncture								
Bai 2012	4.72	5.16	30	1.75	3	30	2.9%	2.97 [0.83, 5.11]
Cai 2016	3.06	4.91	52	1.59	4.19	49	3.1%	1.47 [-0.31, 3.25]
Huang 2008	4.33	3.94	40	1.54	4.24	40	3.1%	2.79 [1.00, 4.58]
Jia et al 2018	6.08	2.31	40	3.22	2.22	39	3.5%	2.86 [1.86, 3.86]
Li 2012	3.25	2.55	48	2.09	2.13	46	3.5%	1.16 [0.21, 2.11]
Li et al 2019	3.14	2.34	40	1.58	2.12	40	3.5%	1.56 [0.58, 2.54]
Lin 2010	10.2	5.88	30	5.9	4.33	30	2.6%	4.30 [1.69, 6.91]
Shao 2016	3.53	5.41	28	1.66	6.41	28	2.4%	1.87 [-1.24, 4.98]
Shi et al 2019	8.88	2.19	55	4.66	2	55	3.6%	4.22 [3.44, 5.00]
Sun 2011	6.74	4.28	30	2.14	2.91	28	3.1%	4.60 [2.73, 6.47]
Sun 2017	3.59	3.65	36	1.72	3.56	36	3.2%	1.87 [0.20, 3.54]
Wang 2015	10.9	3.8	30	10.97	2.67	30	3.2%	-0.07 [-1.73, 1.59]
Wang L et al 2018	4.1	2.63	33	0.6	2.59	31	3.4%	3.50 [2.22, 4.78]
Wang Q et al 2019	4.22	1.9	59	2.75	1.5	59	3.7%	1.47 [0.85, 2.09]
Wang X et al 2019	8.93	3.74	78	4.75	3.96	78	3.4%	4.18 [2.97, 5.39]
Wang Z et al 2017	0.4	1.55	30	-0.04	1.5	30	3.6%	0.44 [-0.33, 1.21]
Yang 2011	3.75	2.91	20	1.15	3.02	20	3.1%	2.60 [0.76, 4.44]
Yang 2014	11.5	5.19	40	5.38	4.35	40	3.0%	6.12 [4.02, 8.22]
Zhai 2012	3.63	2.12	55	0.58	2.56	55	3.6%	3.05 [2.17, 3.93]
Zhang et al 2017	4.19	2.03	42	2.93	1.54	42	3.6%	1.26 [0.49, 2.03]
Subtotal (95% CI)			**816**			**806**	**65.3%**	**2.52 [1.86, 3.18]**
Heterogeneity: Tau² = 1.69; Chi² = 113.68, df = 19 (P < 0.00001); I² = 83%								
Test for overall effect: Z = 7.50 (P < 0.00001)								
1.3.2 electropuncture								
Jiang 2011	3.4	3.88	20	1.3	2.72	20	3.0%	2.10 [0.02, 4.18]
Kang 2011	2.37	2.37	24	0.96	2.28	24	3.4%	1.41 [0.09, 2.73]
Li S et al 2008	11.2	6.61	20	5.4	5.72	20	2.0%	5.80 [1.97, 9.63]
Liu 2015	15.08	1.14	25	8.8	0.96	25	3.7%	6.28 [5.70, 6.86]
Liu 2017	2.53	3.85	19	1.44	3.9	16	2.7%	1.09 [-1.49, 3.67]
Liu J et al 2013	15.14	1.04	32	9.21	0.89	32	3.7%	5.93 [5.46, 6.40]
Ma et al 2018	7.31	3.59	30	3.6	3.67	30	3.1%	3.71 [1.87, 5.55]
Sun et al 2013	4.08	2.31	60	2.01	2.45	60	3.6%	2.07 [1.22, 2.92]
Wang et al 2017	2.14	2.45	35	1.42	2.44	35	3.5%	0.72 [-0.43, 1.87]
Zhou et al 2019	8.1	3.92	60	3.25	3.86	60	3.3%	4.85 [3.46, 6.24]
Zhou H et al 2019	6.72	5.32	40	2.54	4.97	40	2.9%	4.18 [1.92, 6.44]
Subtotal (95% CI)			**365**			**362**	**34.7%**	**3.45 [2.04, 4.87]**
Heterogeneity: Tau² = 4.91; Chi² = 176.15, df = 10 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 4.79 (P < 0.00001)								
Total (95% CI)			**1181**			**1168**	**100.0%**	**2.88 [2.09, 3.66]**
Heterogeneity: Tau² = 4.29; Chi² = 451.98, df = 30 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 7.18 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.38, df = 1 (P = 0.24), I² = 27.3%								

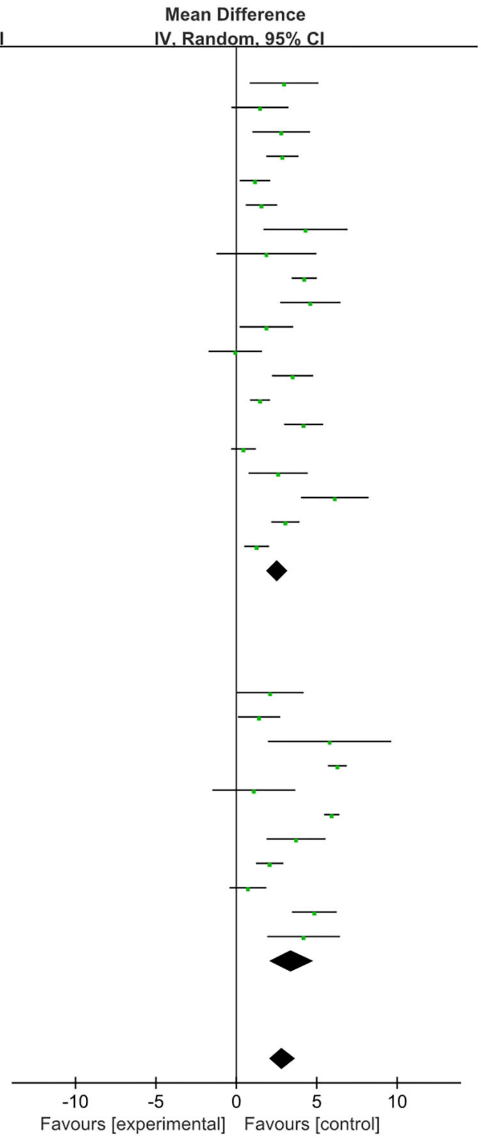

FIGURE 3 | Forest plot comparing the MMSE improved between acupuncture groups and control groups.

conventional rehabilitation done in the control groups in 23 trials, and patients had medicine in control groups in 17 trials. Patients in experiment groups combined the acupuncture or electroacupuncture and conventional rehabilitation or medicine used the same as in control groups in all trials. The merged results showed that synergistic effects of acupuncture or electroacupuncture therapy is clinically significant in improving PSCI, and there were no adverse events/incidents reported in those studies.

There was some inconsistent information in the included studies. The patients were all with ischemic stroke in 10 studies; the other 22 studies included patients with hemorrhage or ischemic stroke, and 4 studies only included post-stroke patients. In the 37 studies, 23 studies indicated that acupuncture treatment was within 6 months from stroke onset, 5 studies was under 1 year, 2 studies was under 14/36 months, and the other 7 studies did not report the accurate time. In this meta-analysis, 24 studies focused on the effects of acupuncture combined with conventional rehabilitation treatment, and the other 13 studies analyzed the effectiveness of acupuncture combined with medicine (Aricept, Xingnaojing, Nimodipine, Piracetam, etc.). Fourteen studies used electroacupuncture, and the other 23 studies used traditional manual acupuncture. The intervention period varied across studies from 2 to 12 weeks.

There were obvious heterogeneities of these articles, so the random effects model was used in this study. Subgroup analysis between acupuncture group and electropuncture did not significantly reduce heterogeneity in this study. This may

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.2.1 acupuncture								
Cai 2016	2.83	6.84	52	1.32	5.81	49	5.3%	1.51 [-0.96, 3.98]
Jia 2011	4.82	4.63	50	3.13	4.84	50	7.3%	1.69 [-0.17, 3.55]
Li et al 2019	4.71	2.36	40	2	1.94	40	11.7%	2.71 [1.76, 3.66]
Lu 2014	3.87	2	30	2.44	2.74	30	10.3%	1.43 [0.22, 2.64]
Sun 2017	7.93	2.46	30	3.32	2.33	28	10.2%	4.61 [3.38, 5.84]
Wang F et al 2014	4.94	3.45	35	2.27	2.98	30	8.6%	2.67 [1.11, 4.23]
Wang L et al 2018	2.9	2.92	64	2.75	31.86	64	0.8%	0.15 [-7.69, 7.99]
Wang Z et al 2017	2.33	2.66	30	-0.3	2.96	30	9.3%	2.63 [1.21, 4.05]
Subtotal (95% CI)			**331**			**321**	**63.5%**	**2.55 [1.71, 3.39]**
Heterogeneity: Tau² = 0.74; Chi² = 15.84, df = 7 (P = 0.03); I² = 56%								
Test for overall effect: Z = 5.95 (P < 0.00001)								
2.2.2 electropuncture								
Feng 2013	8.1	4.95	40	6.83	5.46	40	5.8%	1.27 [-1.01, 3.55]
Liu 2015	5.62	5.68	32	2.2	6.29	30	4.1%	3.42 [0.43, 6.41]
Liu et al 2015	5.32	6.75	19	1.81	7.2	16	2.0%	3.51 [-1.14, 8.16]
Zeng 2015	5.24	5.72	50	4.24	5.74	50	5.9%	1.00 [-1.25, 3.25]
Zhou et al 2019	8.1	3.92	60	3.28	3.68	60	9.6%	4.82 [3.46, 6.18]
Zhou H et al 2019	4.91	3.45	40	2.24	3.23	40	9.1%	2.67 [1.21, 4.13]
Subtotal (95% CI)			**241**			**236**	**36.5%**	**2.81 [1.42, 4.20]**
Heterogeneity: Tau² = 1.64; Chi² = 12.37, df = 5 (P = 0.03); I² = 60%								
Test for overall effect: Z = 3.97 (P < 0.0001)								
Total (95% CI)			**572**			**557**	**100.0%**	**2.66 [1.95, 3.37]**
Heterogeneity: Tau² = 0.88; Chi² = 29.09, df = 13 (P = 0.006); I² = 55%								
Test for overall effect: Z = 7.38 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%								

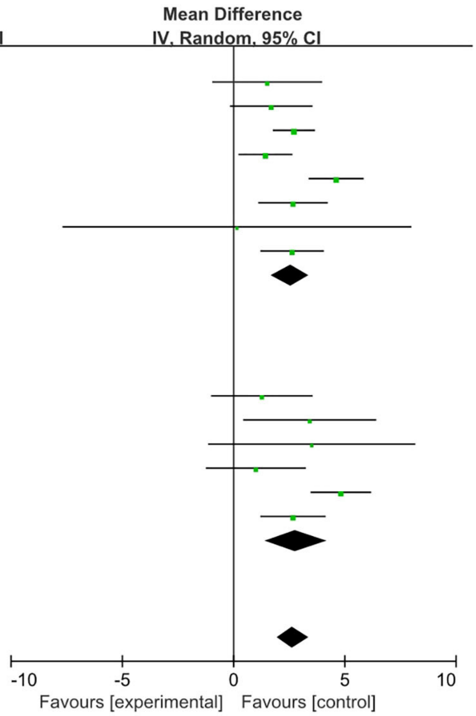

FIGURE 4 | Forest plot comparing the CoMA improved between acupuncture groups and control groups.

be caused by the unbalance of acupoints selection, the different treatment period, and the therapist's technical ability.

In the theoretical system of acupuncture, the Du Meridian is important for the cognitive brain function (Zhou et al., 2013; Liu et al., 2014), and acupoints "Baihui" and "Shenting" belong to the Du Meridian. Baihui and Shenting are both located in the head. To Chinese traditional medicine theoretical system, acupuncture Baihui and Shenting can lift the spirit, clear the mind, and promote resuscitation. In these 37 studies, 26 studies acupuncture the acupoints including "Baihui," and 19 studies involved the acupoint "Shenting" for the treatment of mental and emotional illness. Other acupoints, such as Feishu, Xinshu, Ganshu, Shenshu, and Pishu were shown involving the cognitive function in more than three studies. Other acupuncture points involved were Huiyin, Yintang, Neiguan, Yanglingquan, Taixi, Zulinqi, Sishencong, Fengchi, Fengfu, Gongxue, Yiming, Guanyuan, Taichong, Shenshu, Benshen, Hegu, Taichong, Fengshi, Quchi, Zusanli, Sanyingjiao, Xuehai, Renzhong, Shenmen, etc.

Acupuncture improves cognitive function and depressive disorder, because acupuncture on stroke patients can improve neurological function (Chen et al., 2018; Hung et al., 2019). Animal studies showed that acupuncture with Baihui may have a neuroprotective effect via decreasing MMP-9 expression or improving the endothelial nitric oxide synthase (eNOS)-mediated perfusion (Dong et al., 2009; Kim et al., 2013).

H Jiang et al.'s and J Liang et al.'s studies showed that acupuncture was associated with the potential of DNA methylation and histone modifications of brain-derived neurotropic factor in epigenetic mechanism, which can produce antidepressant effect in rats (Liang et al., 2012; Jiang et al., 2018). F Taya et al. showed that acupuncture may increase cerebral collateral circulation, promoting repair of the lesion (Taya et al., 2015). P.Y. Sun et al. showed that acupuncture repairs hippocampal neuronal damage, which is probably related to the contents of hippocampal monoamine neurotransmitters (NE, 5-HT and DA) (Sun et al., 2019). Other studies showed that electropuncture can improve cognitive function via synaptic plasticity by attenuating pathological lesions and increasing the density of dendritic spines and number of CA1 synapses in rats (Lin et al., 2016; Liu et al., 2017; Wen et al., 2018).

The selection criteria for the assessment of cognitive function were the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). MMSE is an effective tool that can be used to systematically and thoroughly assess mental status, which was validated and extensively used from 1975 (Foreman et al., 1996). MoCA is a widely used screening assessment for detecting cognitive impairment since 1996, which was validated in the setting of mild cognitive impairment (Nasreddine et al., 2005). There are other internationally recognized examinations of cognitive impairment including NCSE, NIHSS, LOTCA, HDS, and cognitive potential 300, but the most commonly used indicators are MMSE and MoCA. We restricted the inclusion criteria to a consistent standard of outcome assessing with MMSE or MoCA, so the number of RCTs included in this study was not so many

Acupuncture compared to conventional treatment for improving post strok cognitive impairment

Patient or population: Post strok patients
Setting: Peking University Shenzhen Hospital
Intervention: Acupuncture
Comparison: Conventional treatment

Outcomes	Anticipated absolute effects* (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with conventional treatment	Risk with acupuncture		
Mental state improved (MMSE) assessed with: MMSE form follow up: 2-12 weeks	The mean mental state improved was **2.96** [a]	MD **2.88 higher** (2.09 higher to 3.66 higher)	3971 (31 RCTs)	⊕⊕⊕◯ MODERATE
Cognitive assessment improved (MoCA) assessed with: MoCA form follow up: 4-12 weeks	The mean cognitive assessment improved was **2.68** [b]	MD **2.66 higher** (1.95 higher to 3.77 higher)	1129 (14 RCTs)	⊕⊕⊕◯ MODERATE [c]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. After conventional treatment, the MMSE score was improved by 2.97 than before.
b. After conventional treatment, the MoCA score was improved by 2.68 than before.
c. Many of the RCTs were low quality with an inadequate level of blinding because blindings in the acupuncture therapy were difficult for the therapists and patients.

FIGURE 5 | Evidence profile.

(only 37), but the results of meta-analyses were more clear and definite, and the quality of evidence was assessed to be moderate.

About the limitation, firstly, all studies were done in China, although the Cai et al. (2016) study was published in the English language. There might have been additional reports using non-Chinese or non-English languages that were not included which may limit the results of the study. Secondly, many of the trials were of low quality with an inadequate level of blinding; although blinding in the acupuncture therapy is difficult for the therapists and patients, blinding the assessor is necessary.

Despite these limitations, conclusions can be drawn from the results of our study.

CONCLUSIONS

Acupuncture therapy has positive synergistic effects in improving PSCI, but more rigorous design studies with large-scale sham are needed to determine the longevity of acupuncture effects.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

LZ, QW, and XL: conceptualization and writing, review, and editing. LZ, YW, and JQ: data curation and methodology. LZ and XL: funding acquisition. QW and XL: supervision. LZ: writing the original draft. All authors contributed to the article and approved the submitted version.

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Physical Activity for Executive Function and Activities of Daily Living in AD Patients: A Systematic Review and Meta-Analysis

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Objectives: The present study aimed to systematically analyze the effects of physical activity on executive function, working memory, cognitive flexibility, and activities of daily living (ADLs) in Alzheimer's disease (AD) patients and to provide a scientific evidence-based exercise prescription.

Methods: Both Chinese and English databases (PubMed, Web of Science, the Cochrane Library, EMBASE, VIP Database for Chinese Technical Periodicals, China National Knowledge Infrastructure, and Wanfang) were used as sources of data to search for randomized controlled trials (RCTs) published between January 1980 and December 2019 relating to the effects of physical activity on executive function, working memory, cognitive flexibility, and ADL issues in AD patients. Sixteen eligible RCTs were ultimately included in the meta-analysis.

Results: Physical activity had significant benefits on executive function [standard mean difference (SMD) = 0.42, 95% confidence interval (CI) 0.22–0.62, $p < 0.05$], working memory (SMD = 0.28, 95% CI 0.11–0.45, $p < 0.05$), cognitive flexibility (SMD = 0.23, 95% CI −0.02 to 0.47, $p < 0.01$), and ADLs (SMD = 0.68, 95% CI 0.19–1.16, $p < 0.05$) among AD patients. Subgroup analysis indicated that, for executive function issues, more than 60 min per session for 16 weeks of moderate-to-high-intensity dual-task exercises or multimodal exercise had a greater effect on AD patients. For working memory and cognitive flexibility issues, 60–90 min of moderate-intensity dual-task exercises 1–4 times/week was more effective. For ADL issues, 30–90 min of multimodal exercise at 60–79% of maximal heart rate (MHR) 3–4 times/week had a greater effect on AD patients.

Conclusions: Physical activity was found to lead to significant improvements in executive function, working memory, cognitive flexibility, and ADLs in AD patients and can be used as an effective method for clinical exercise intervention in these patients. However, more objective, scientific, and effective RCTs are needed to confirm this conclusion.

Keywords: exercise prescription, ADL, executive function, AD, physical activity

INTRODUCTION

Alzheimer's disease (AD) is a common disorder of the nervous system, accounting for disease in 60–70% of patients with dementia (Reitz et al., 2011), causing severe clinical, social, and economic problems (Prince et al., 2013). Features of dementia include progressive cognitive decline, including loss of memory, language, or executive function, and subsequent decline of social function, for example, activities of daily living (ADLs) (Allal et al., 2015). The cognitive process of the frontal lobe may also change, which is characterized by decreased attention and executive function, as evidenced by deficits in problem solving, planning, and organizing behavior and ideas, abstraction, judgment, cognitive flexibility, decision making, working memory, and self-monitoring (Avilla and Miotto, 2002; Yaari and Bloom, 2007). By 2050, the number of people ≥60 years old will increase by 1.25 billion (Prince et al., 2013), and there will be an estimated 115.4 million people with dementia (Maffei et al., 2017). Drug therapy has been shown to be beneficial to the cognitive function and dependence in ADLs in AD patients (Tan et al., 2014), but it also has side effects.

Based on the above factors, alternative treatment options for AD are necessary to achieve better treatment results. Some research shows that approximately one-third of all AD cases may be due to potentially modifiable factors, such as lack of physical activity (Norton et al., 2014), which means that the disease can be prevented. Furthermore, some human and animal studies have shown that physical activity can promote the improvement of cerebrovascular function, perfusion, and brain neural plasticity, which can prevent the gradual loss of cognitive function or executive function related to diseases, such as aging and dementia (Davenport et al., 2012; Erickson et al., 2012). Furthermore, physical activity is considered to have a significant effect on executive function (Wilbur et al., 2012), as confirmed recently in a large experiment of moderate-intensity exercise in sedentary older adults: in the subgroup with the weakest cognitive ability, executive function was improved. In recent years, more and more studies have confirmed the positive effect of physical activity among AD patients. Meanwhile, executive function can directly affect the ADLs or continued independence (Royall et al., 2000; Bell-McGinty et al., 2002; Cahn-Weiner et al., 2002). Some studies provide support for the hypothesis that commonly used clinical trials of executive function significantly predict the ADLs (Bell-McGinty et al., 2002; Cahn-Weiner et al., 2002). As such, with a decrease in executive function, a breakdown in successful execution and completion of complex behavioral procedures is likely, especially in subsets of ADLs involving executive control (Bell-McGinty et al., 2002). However, some ADLs (e.g., ambulating, cooking, reading, leisure, housework, and managing finances) promote improved physical, cognitive, and executive functions (Bell-McGinty et al., 2002; Cahn-Weiner et al., 2002; Jekel et al., 2015). More and more studies have shown that physical activity has a significant impact on improving executive function and ADL issues in AD patients, thus improving their quality of life. In addition, the World Health Organization (WHO) recommends that people over the age of 65 should take at least 150 min of moderate-intensity aerobic exercise (such as brisk walking and jogging) every week, 75 min of high-intensity aerobic exercise every week, or a combination of the two supplemented by muscle-strengthening activities (such as resistance exercise and stretching exercise) on 2 or more days every week (World Health Organization Physical Activity Older Adults, 2017).

Recently, a great deal of research has been carried out to evaluate the impact of physical activity on executive function or ADL issues among AD patients. Because of the differences in the intervention samples, timing, frequency, intensity, and duration, the specific effects on executive function and ADL issues among AD patients could have been different. Therefore, the aim of our meta-analysis was to evaluate the impact of physical activity on executive function and ADL issues in AD patients. Moreover, executive function is a complex construct that includes different functions, such as cognitive flexibility inhibition and working memory. However, there are few studies on inhibitory functions in AD patients. Therefore, this study assessed the specific effects of physical activity on cognitive flexibility and working memory issues in AD patients. This study also explored the internal regulation mechanism of physical activity on the executive functions of AD patients to provide a corresponding exercise prescription.

METHODS

Search Strategy

Literature was identified using the following databases: PubMed, Web of Science, the Cochrane Library, EMBASE, VIP Database for Chinese Technical Periodicals, China National Knowledge Infrastructure, and Wanfang. These databases were searched to identify randomized controlled trials (RCTs) published in any language between January 1, 1980 and December 31, 2019. The search terms used included "exercise or physical activity or aerobic exercise or physical exercise or aerobic fitness or walking or cycling or strength training or balance training or flexibility training" with AD terms including "AD or Alzheimer's disease or Alzheimer" as well as "executive function or executive functions or ADL or activities of daily living."

Inclusion Criteria

The selection criteria were as follows: (1) RCTs investigating the impact of any type of physical activity as an additional intervention on executive function or ADLs; (2) sample population including a group of old people (aged ≥50 years) and participants diagnosed with Alzheimer's-type dementia of any severity, excluding diagnoses of other dementias or mild cognitive impairment (MCI); (3) interventions in an experimental group involving physical activity (e.g., aerobic exercise, aerobic fitness, walking, cycling, strength training, balance training, and flexibility training) compared with different types of control groups (e.g., usual care, no physical activity, and no-intervention control group); (4) outcome indicators including test data on executive function and ADLs; and (5) publication language of Chinese or English.

Exclusion Criteria

The exclusion criteria were as follows: (1) duplicated studies; (2) reviews, observational studies, abstract-only articles (without full-text article available), and non-RCT studies; and (3) studies with no data or unclear data reported for analysis.

Collection of Studies

Two investigators (LZ and LW) independently reviewed the titles and abstracts from the search results and screened out the full texts that might meet the criteria. If a study met the inclusion criteria, it received a full-text article evaluation. When there was any disagreement between the two reviewers, a third reviewer (LL) was invited to discuss with them and to verify the eligibility of the uncertain article. All eligible studies included information, such as author, publication year, country, sample size, sample population age, intervention methods, duration, measurement standards, experimental results, and dropouts.

Data Extraction

Detailed information included the first author, publication year, participant characteristics (sample size and age range/mean age), intervention design (frequency, duration of each intervention session, duration, and follow-up), outcome measure, statistical analyses, and results. Meanwhile, we also extracted quantitative data from the research results: mean and standard deviation (SD) of executive function and ADLs between physical activity and usual care, including its corresponding sample size.

Methodological Quality Assessment

Two authors used the modified the Physical Therapy Evidence Database (PEDro) scale (Zou et al., 2019) to independently perform methodological quality assessment of each eligible study. This assessment consisted of nine items (randomization, concealed allocation, similar baseline, blinding of assessors, ≤15% dropouts, intention-to-treat analysis, between-group comparison, point measure and measures of variability, and isolate exercise intervention), and higher scores indicate better quality of the method.

Statistical Analysis

Stata 14.0 (StataCorp, Texas, USA) was used to calculate effect sizes [standardized mean difference (SMD)] of physical activity

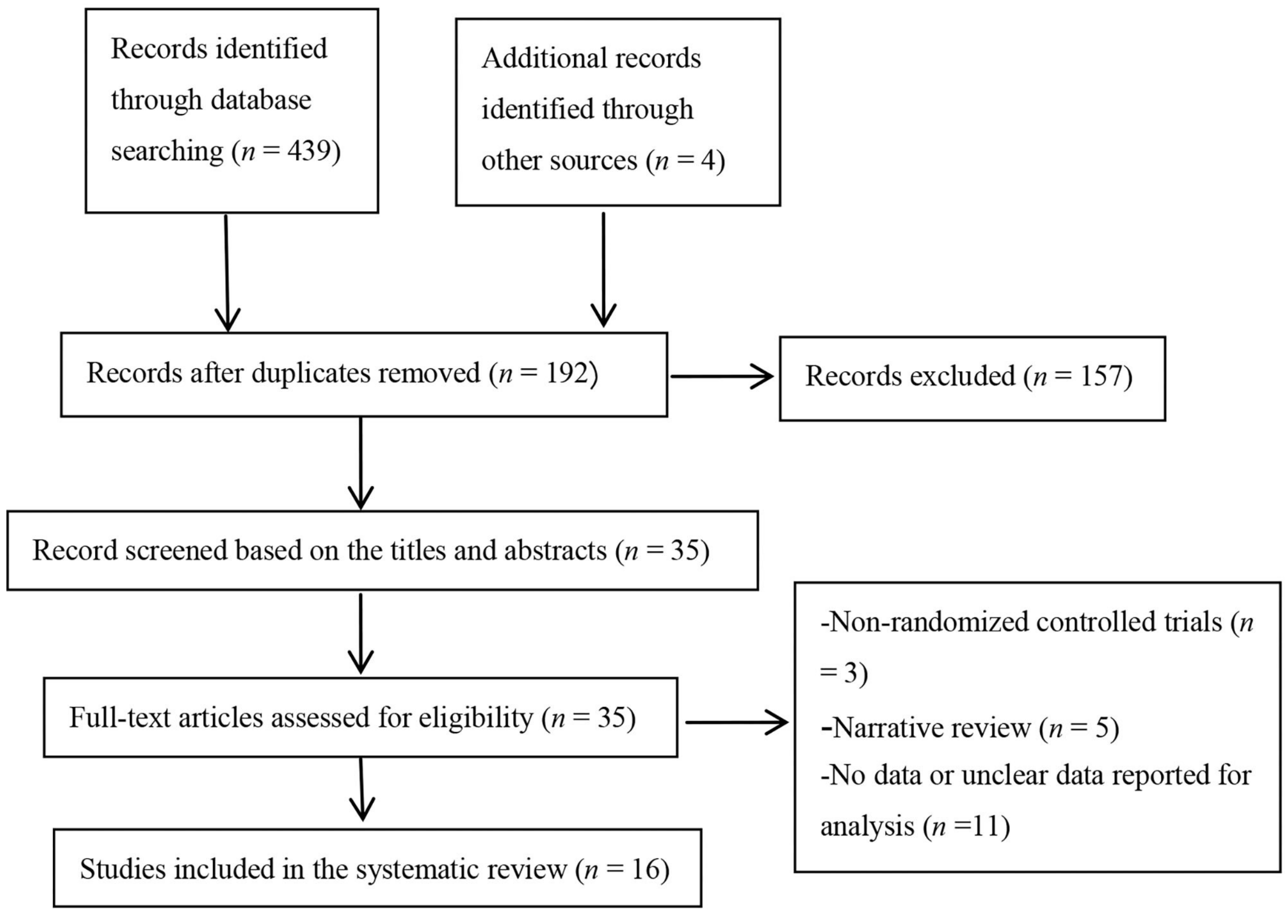

FIGURE 1 | Flowchart of study selection.

TABLE 1 | Summary characteristics of the included studies.

References	Country	Sample size (attrition rate)	Mean age or age range	Duration (W)	Experimental group intervention	Control group intervention	Outcome assessments	Follow-up
Morris et al. (2017)	US	76 (10.5%)	T = 74.4 (6.7) C = 71.4 (8.4)	26	AEx: 150 min/week of moderate-intensity aerobic exercise (cycling, walking, arm cranking on a specific ergometer)	ST: stretching and toning control program	EF	No
Fonte et al. (2019)	Italy	41 (0%)	T = 79 (9) C = 79 (7)	24	3 × 90 min/week moderate-intensity endurance and resistance training	Standard treatment	FAB/IADL	Yes
Ohman et al. (2016)	Helsinki	140 (21%)	T = 77.7 (5.4) C = 78.1 (5.3)	48	2 × 60 min/week executive function-related exercises, dual-task training, and balance, endurance, or aerobic exercises	Usual care	CDT/VF	No
Tootsa et al. (2017)	Sweden	186 (13.4%)	T = 84.4 (6.2) C = 85.9 (7.8)	16	3 × 45 min/week high-intensity functional exercise (HIFE) program (weight-bearing exercises, strength exercises, balance training)	Regular daily life	VF	No
Pedroso et al. (2017)	Brazil	42 (14.2%)	T = 77.6 (6.2) C = 79.2 (5.6)	12	3 × 60 min/week functional-task training: warm-up exercise period (walking, stretching exercises) + stimulated locomotion (walking up and down the stairs, zigzag jogging, etc.) + stimulate other activities of daily living (sitting down and getting up, moving objects)	Standard medical care	VF/DAFS-R	No
Holthoff et al. (2015)	Germany	30 (0%)	T = 72.4 (4.3) C = 70.6 (5.4)	12	3 × 30 min/week PA intervention program: motor-assisted or active resistance training of the legs on a movement trainer	Usual care	EF/ADCS-ADLs	Yes
Coelho et al. (2012)	Brazil	27 (0%)	T = 78 (7.3) C = 77.1 (7.4)	16	3 × 60 min/week multimodal exercise (strength/resistance exercises, agility, flexibility, strength, balance, and cognitive training)	Regular daily life	FAB/CDT	No
Silvaa et al. (2019)	Brazil	27 (0%)	T = 81.2 (8.8) C = 77.5 (8.0)	12	2 × 60 min/week multimodal training session (balance training, aerobic exercise, strength training)	Usual care	CDT/VF	No
Andrade et al. (2013)	Brazil	30 (0%)	T = 78.6 (7.1) C = 77.0 (6.3)	16	3 × 60 min/week multimodal exercise (warm-up, aerobic work, dual-task activities)	Usual care	EF/CDT	No
El-Kader and Al-Jiffr (2016)	Saudi Arabia	59 (32.2%)	T = 68.9 (5.7) C = 69.1 (6.1)	8	3 × 45 min/week aerobic exercise (warm-up, stretching exercises, aerobic exercise, cooling down [on treadmill with low speed and without inclination])	Usual treatment	SF-36PF	No
Rolland et al. (2017)	France	134 (17.9%)	T = 82.8 (7.8) C = 83.1 (7.0)	48	2 × 60 min/week aerobic, strength, flexibility, and balance training	Routine medical care	ADLs	No
Vreugdenhill et al. (2012)	Australia	40 (0%)	T = 73.5 (51–83) C = 74.7 (58–89)	16	7 × 30 min/week strength and balance training and brisk walking + usual treatment	Usual treatment	Barthel Index/IADL	Yes

(Continued)

TABLE 1 | Continued

References	Country	Sample size (attrition rate)	Mean age or age range	Duration (W)	Experimental group intervention	Control group intervention	Outcome assessments	Follow-up
Venturelli et al. (2011)	Italy	24 (14.3%)	T = 83 (6) C = 85 (5)	24	4 × 30 min/week moderate exercise (walking)	Routine care	Barthel Index	No
Vidoni et al. (2017)	Italy	65 (0%)	T = 74.1 (6.8) C = 71.1 (8.8)	26	AEx: 150 min/week of moderate-intensity aerobic exercise	ST: stretching and toning control program	BADL/IADL	No
Hoffmanna et al. (2016)	Denmark	200 (5%)	T = 69.8 (7.4) C = 71.3 (7.3)	16	3 × 30 min/week moderate-to-high-intensity aerobic exercise (ergometer bicycle, cross trainer, treadmill)	Usual treatment	SDMT/ADCS-ADLs	No
Chang et al. (2015)	China	60 (5%)	T = 70.7 (7.4) C = 70.2 (8.5)	16	3 × 60–90 min/week cycling or treadmill + routine medical care	Routine medical care	ADCS-ADLs	No

W, week; EF, executive function; AEx, aerobic exercise condition; ST, stretching and toning control condition; FAB, Frontal Assessment Battery; IADL, instrumental activity of daily living; CDT, clock-drawing test; VF, verbal fluency test; DAFS-R, Direct Assessment of Functional Status; ADCS-ADLs, Alzheimer's Disease Cooperative Study—Activities of Daily Living; SDMT, Symbol Digit Modalities Test; SF-36PF, SF-36: Physical Functioning; BADL, basic instrumental activities of daily living.

on executive function and ADLs. SMD was considered as small (0.2–0.49), moderate (0.5–0.79), or large (0.8). According to the intervention system review of the Cochrane Collaboration handbook, selection of fixed-effects or random-effects meta-analysis should be based on the actual effect of an intervention on outcome measures. Differences (standard mean difference, SMD) and 95% confidence intervals (95% CIs) were calculated. I^2 values of 25, 50, and 75% are considered to be low, medium, and high heterogeneity (Higgins et al., 2003). When the heterogeneity test $I^2 \geq 50\%$, a random-effects model was used for meta-analysis. In this study, regression analysis was used to study the degree of experimental heterogeneity. Subgroup analyses were performed according to categorical variables, including sample age, exercise intensity, frequency, duration, duration of each intervention session, and exercise type. Subgroup analysis was used to determine which subgroup was more effective for improving the executive function and ADLs among AD patients.

RESULTS

Study Selection

A total of 443 topic-related articles were identified from 7 databases and other resources (**Figure 1**). After removing duplicate articles, 192 articles remained. A total of 157 articles were deleted after titles and abstracts were screened for non-related articles ($n = 148$) and abstract-only articles ($n = 9$). The remaining 35 articles were further screened after reading the full-text articles. Nineteen studies were removed because they were non-RCTs ($n = 3$), reviews ($n = 5$), or had no or unclear outcome measures ($n = 11$). Finally, our meta-analysis included 16 eligible studies.

Characteristics of Eligible Studies

There were 16 eligible (Venturelli et al., 2011; Coelho et al., 2012; Vreugdenhill et al., 2012; Andrade et al., 2013; Chang et al., 2015; Holthoff et al., 2015; El-Kader and Al-Jiffr, 2016; Hoffmanna et al., 2016; Ohman et al., 2016; Morris et al., 2017; Pedroso et al., 2017; Rolland et al., 2017; Tootsa et al., 2017; Vidoni et al., 2017; Fonte et al., 2019; Silvaa et al., 2019) RCTs, as shown in **Table 1**. There were 1,181 participants in total; the smallest sample was 27 participants (Silvaa et al., 2019), and the largest sample was 200 participants (Holthoff et al., 2015). The age of the participants in the experiment ranged from 50 to 96 years old. The shortest experimental period was 8 weeks (El-Kader and Al-Jiffr, 2016), and the longest experimental period was 1 year (Rolland et al., 2017). The experimental group included various interventions, such as moderate-to-high-intensity physical activity, ergometer bicycle exercise, walking, cycling, strength training, balance training, and flexibility training. The control group was treated by usual care, standard treatment, routine medical care, etc. (**Table 1**).

Methodological Quality Assessment

The methodological quality score for all qualified studies was between 5 and 8 (**Table 2**). All studies were RCTs and had similar baseline characteristics, between-group comparisons, point measures, measures of variability description, and

TABLE 2 | Quality evaluation of eligible randomized controlled trials.

References	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Score
Morris et al. (2017)	1	0	1	0	1	0	1	1	1	6
Fonte et al. (2019)	1	1	1	1	1	0	1	1	1	8
Ohman et al. (2016)	1	0	1	0	0	0	1	1	1	5
Tootsa et al. (2017)	1	1	1	1	1	0	1	1	1	8
Pedroso et al. (2017)	1	0	1	0	1	0	1	1	1	6
Holthoff et al. (2015)	1	0	1	0	1	0	1	1	1	6
Coelho et al. (2012)	1	0	1	0	1	0	1	1	1	6
Silvaa et al. (2019)	1	0	1	0	1	0	1	1	1	6
Andrade et al. (2013)	1	0	1	0	1	0	1	1	1	6
El-Kader and Al-Jiffr (2016)	1	0	1	0	0	0	1	1	1	5
Rolland et al. (2017)	1	1	1	1	0	1	1	1	1	8
Vreugdenhill et al. (2012)	1	0	1	0	1	0	1	1	1	6
Venturelli et al. (2011)	1	1	1	1	1	0	1	1	1	8
Vidoni et al. (2017)	1	0	1	0	1	0	1	1	1	6
Hoffmanna et al. (2016)	1	0	1	0	1	0	1	1	1	6
Chang et al. (2015)	1	0	1	0	1	0	1	1	1	6

Item 1, randomization; Item 2, concealed allocation; Item 3, similar baseline; Item 4, blinding of assessors; Item 5, <15% dropouts; Item 6, intention-to-treat analysis; Item 7, between-group comparison; Item 8, point measure and measures of variability; Item 9, isolate exercise intervention; 1, explicitly described and present in details; 0, absent, inadequately described, or unclear.

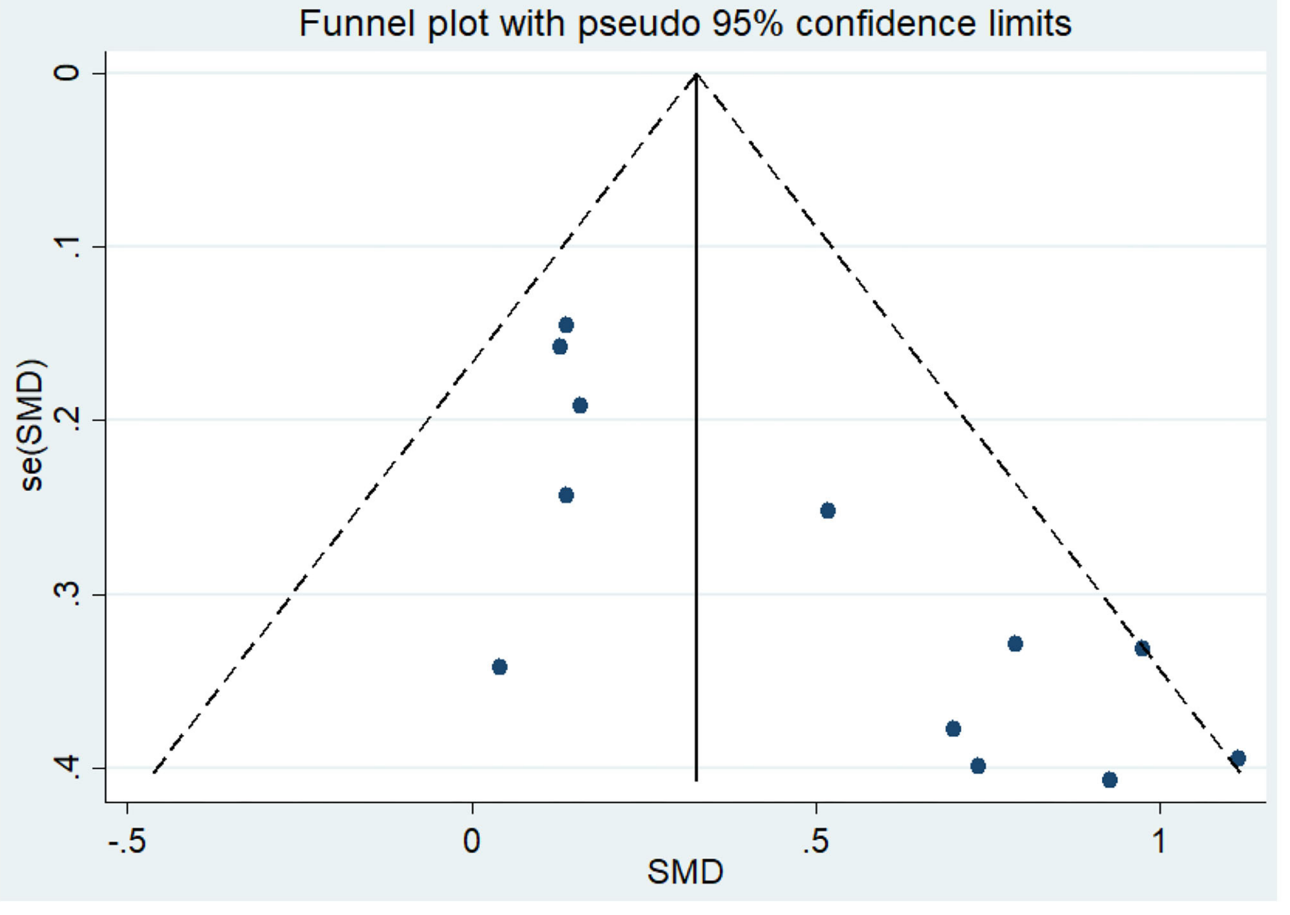

FIGURE 2 | Funnel plot of publication bias for executive function.

isolated exercise interventions. Only four studies had concealed allocations and blinding of assessors (Venturelli et al., 2011; Rolland et al., 2017; Tootsa et al., 2017; Fonte et al., 2019). The dropout rates in three of these studies were all higher than 15% (El-Kader and Al-Jiffr, 2016; Ohman et al., 2016; Rolland et al., 2017), and only one study used the intention-to-treat principle (Rolland et al., 2017).

Meta-Analysis of Outcome Indicators

Effect of Physical Activity on Executive Function Issues in AD Patients

Twelve articles (Coelho et al., 2012; Vreugdenhill et al., 2012; Andrade et al., 2013; Holthoff et al., 2015; Hoffmanna et al., 2016; Ohman et al., 2016; Morris et al., 2017; Pedroso et al., 2017; Tootsa et al., 2017; Vidoni et al., 2017; Fonte et al., 2019; Silvaa et al., 2019) compared the effects of an intervention group and a control group on executive function before and after the experiment. An asymmetrical funnel plot was presented. The funnel plot shows that there were no outlier values (**Figure 2**). There was a moderate heterogeneity in the research literature ($p = 0.047$, $I^2 = 44.8\%$), and a random-effects model was selected for the meta-analysis (**Figure 3**). The meta-analysis of 12 studies demonstrated that physical activity had significant effects on improving executive function in AD patients (SMD = 0.42, 95% CI 0.22–0.62, $p < 0.05$).

Covariates including age, intensity, frequency, time, and duration are likely to be the influencing factors for executive

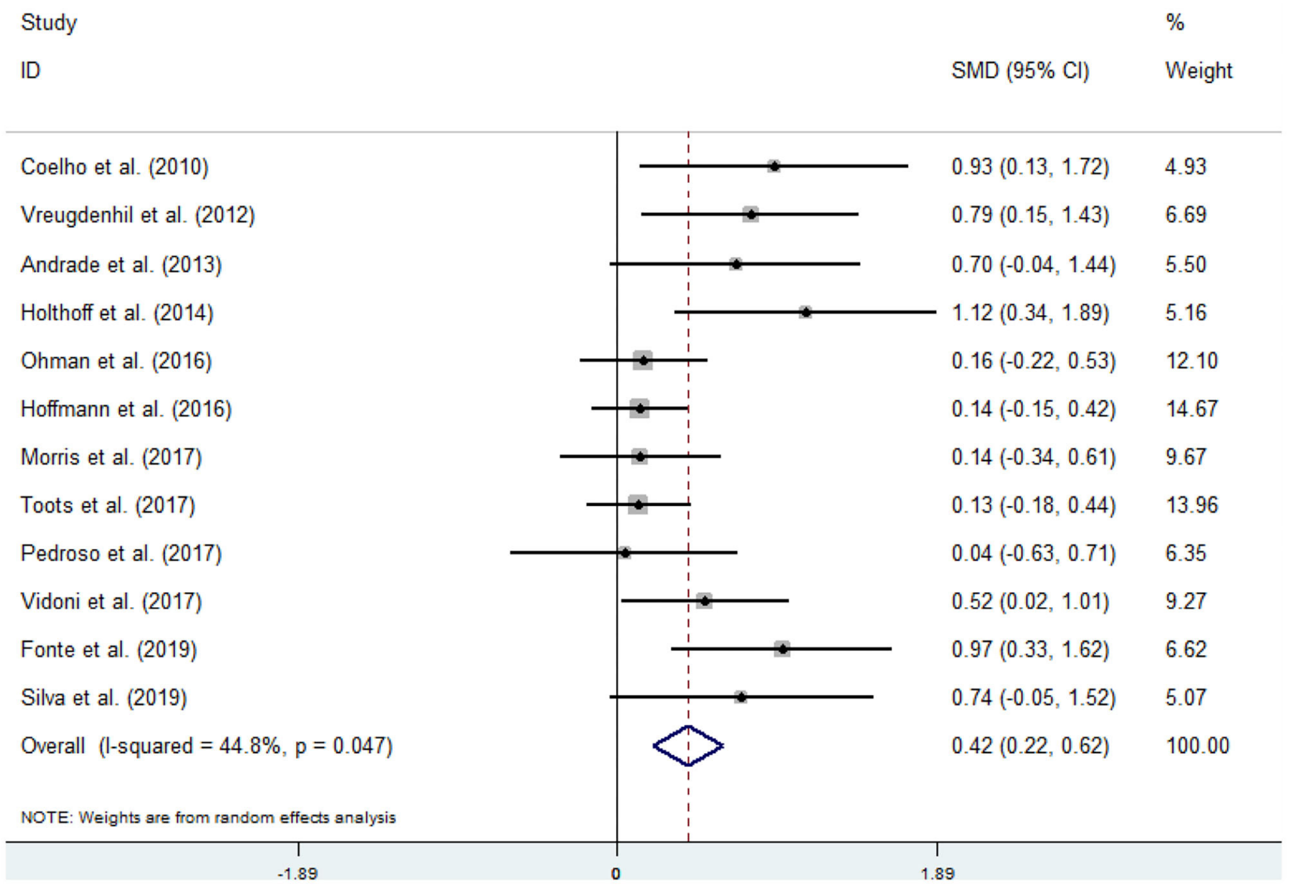

FIGURE 3 | Effect of physical activity on executive function.

TABLE 3 | Covariate regression analysis of executive function issues in AD patients.

_ES	Coef.	Std. err.	*t*	*p* > *t*	(95% CI)	
Age	0.0110741	0.0218454	0.51	0.63	−0.0423797	0.0645279
Intensity (%)	−0.0271544	0.0123192	−2.20	0.07	−0.0572985	0.0029897
Frequency (times/week)	0.1126148	0.0999144	1.13	0.303	−0.131867	0.3570966
Time (min)	0.0037139	0.0031768	1.17	0.287	−0.0040595	0.0114874
Duration (week)	−0.0245532	0.0129349	−1.9	0.106	−0.0562039	0.0070974
_cons	1.441027	1.818227	0.79	0.458	−3.008015	5.890069

TABLE 4 | Subgroup analysis of executive function issues in AD patients.

Group	Subgroup	*N*	SMD	95% CI	*p*	I^2
Age	65–75	5	0.44	0.109, 0.771	0.065	54.80%
	Older than 75	7	0.424	0.136, 0.713	0.086	45.80%
Intensity (%)	35–59	2	0.574	−0.356, 1.505	0.029	79.00%
	60–79	8	0.549	0.303, 0.794	0.293	17.40%
	80–89	2	0.134	−0.076, 0.343	0.968	0.00%
Frequency (times/week)	1–2 times/week	4	0.293	0.052, 0.534	0.403	0.00%
	3–4 times/week	7	0.473	0.155, 0.790	0.021	59.70%
	5–7 times/week	1	0.79	0.145, 1.435	—	—
Time (min)	30≤min<60	3	0.604	−0.023, 1.231	0.022	73.90%
	60≤min<90	7	0.424	0.136, 0.713	0.086	45.80%
	90≤min≤150	2	0.322	−0.049, 0.694	0.279	14.80%
Duration (week)	8–12 weeks	3	0.606	−0.033, 1.244	0.107	55.20%
	16 weeks	5	0.269	0.082, 0.692	0.047	44.80%
	24–48 weeks	4	0.387	0.051, 0.724	0.124	47.90%
Event	Single exercises	1	1.115	0.342, 1.888	—	—
	Dual-task exercises	3	0.492	−0.003, 0.988	0.144	48.3%
	Multimodal exercise	8	0.345	0.123, 0.567	0.111	40.1%

"—" heterogeneity test cannot be conducted due to the lack of literature.

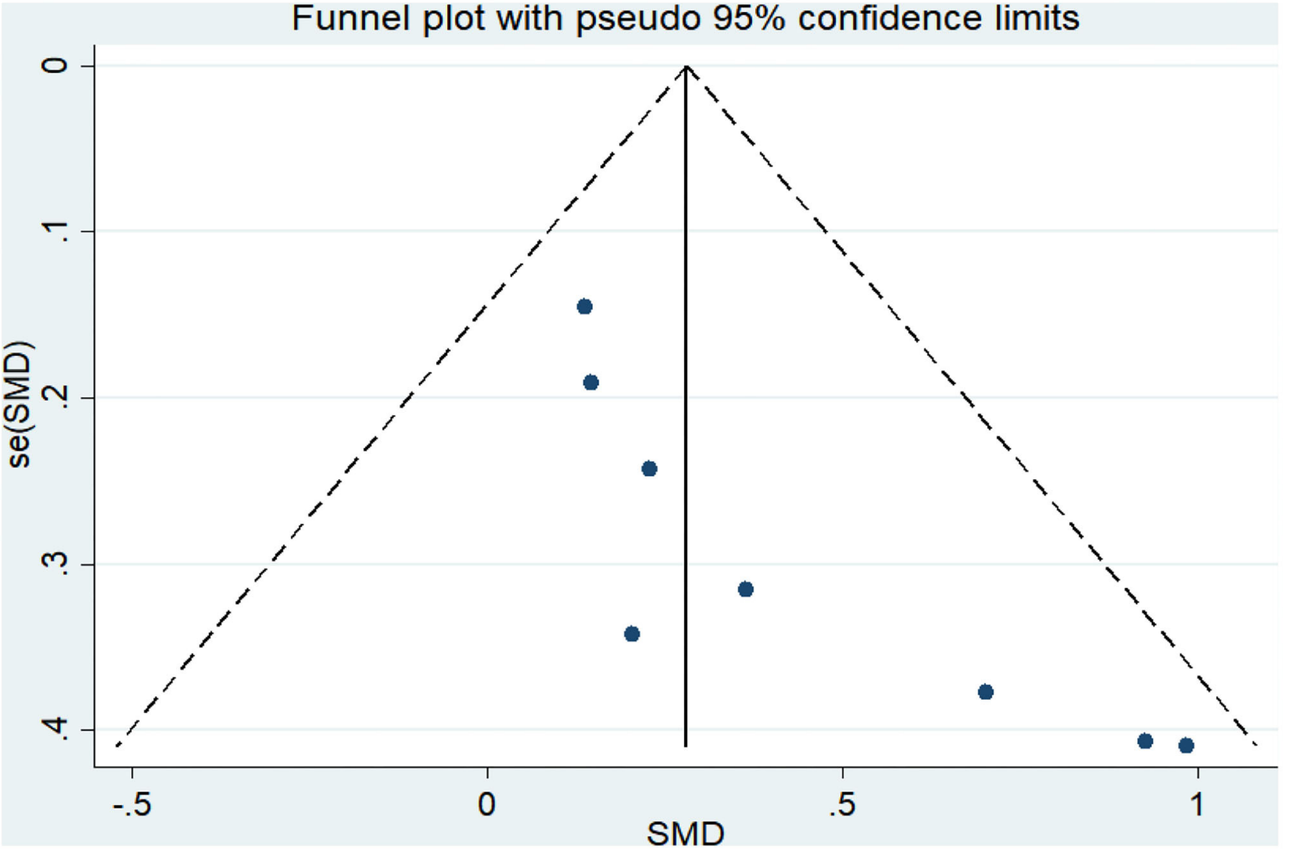

FIGURE 4 | Funnel plot of publication bias for working memory.

function issues in AD patients. The results of the regression of covariates for executive function issues in AD patients are presented in **Table 3**. For executive function, there were no significant effects of age (95% CI −0.0423797 to 0.0645279, $p = 0.63$), intensity (95% CI −0.0572985 to 0.0029897, $p = 0.07$), frequency (95% CI −0.131867 to 0.3570966, $p = 0.303$), time (95% CI −0.0040595 to 0.0114874, $p = 0.287$), or duration (95% CI −0.0562039 to 0.0070974, $p = 0.106$).

According to the sample population's age, exercise intensity, frequency, time, and duration, this study divided the research subjects into different subgroups, as shown in **Table 4**. The results from the subgroup analysis are as follows: (1) age: physical activity was beneficial for AD patients who were older than 75 years and had executive function issues. (2) Intensity: for executive function issues in AD patients, maintaining a 60–79 or an 80–89% maximal heart rate (MHR) during physical activity was more effective. (3) Frequency: the frequency of physical activity has a significant impact on the improvement of the executive function in AD patients, and the effect of 1–2 times/week was better than the effect of 3–4 or 5–7 times/week. (4) Time: a total of 60–150 min of physical activity per exercise session significantly improved executive function in AD patients. (5) Duration: an intervention duration of 16 or 24–48 weeks showed a significant effect on executive function issues in AD patients. (6) Event: for executive function issues in AD patients, both dual-task exercises and multimodal exercise had significant effects.

Effect of Physical Activity on Working Memory Issues in AD Patients

Eight articles (Coelho et al., 2012; Andrade et al., 2013; Hoffmanna et al., 2016; Ohman et al., 2016; Morris et al., 2017; Pedroso et al., 2017; Fonte et al., 2019; Silvaa et al., 2019) evaluated the effects of physical activity on working memory issues in AD patients. An asymmetrical funnel plot was presented. The funnel plot shows that there were no outlier values (**Figure 4**). The heterogeneity test results of the included research literature were not significant ($p = 0.303$, $I^2 = 16.1\%$); thus, the fixed-effects model was used for meta-analysis (**Figure 5**). The meta-analysis of eight studies demonstrated that physical activity had significant effects on improving working memory in AD patients (SMD = 0.28, 95% CI 0.11–0.45, $p < 0.05$).

The results of the regression of covariates for cognitive flexibility issues in AD patients are presented in **Table 5**. For cognitive flexibility, there were no significant effects of age (95% CI −0.1637734 to 0.2960517, $p = 0.341$), intensity (95%

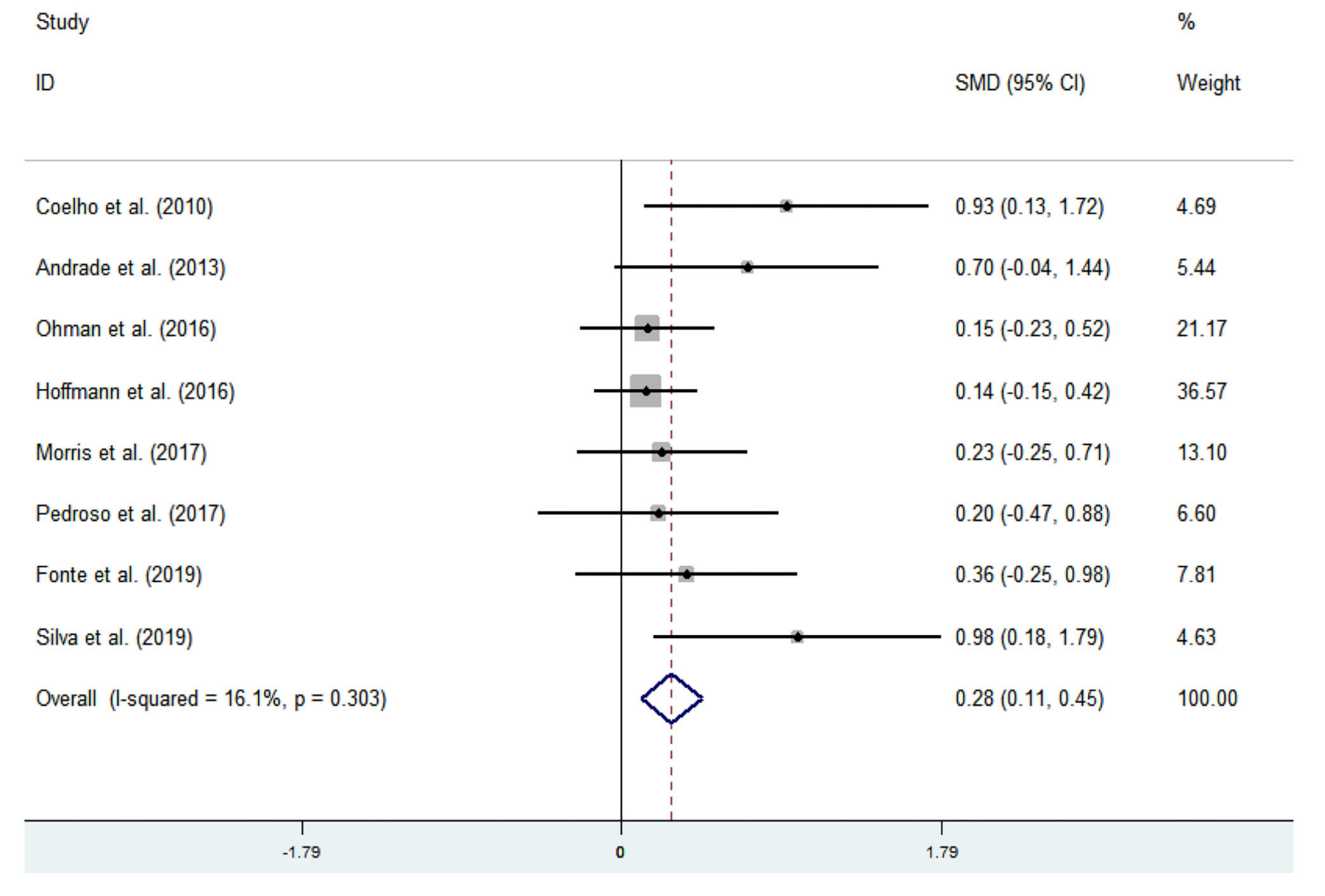

FIGURE 5 | Effect of physical activity on working memory.

TABLE 5 | Covariate regression analysis of working memory issues in AD patients.

_ES	Coef.	Std. err.	*t*	*p* > *t*	(95% CI)	
Age	0.0661391	0.0534351	1.24	0.341	−0.1637734	0.2960517
Intensity (%)	0.0060079	0.0481411	0.12	0.912	−0.2011265	0.2131423
Frequency (times/week)	−0.2336269	0.3742413	−0.62	0.596	−1.843857	1.376603
Time (min)	−0.0029123	0.0065205	−0.45	0.699	−0.0309679	0.0251433
Duration (week)	−0.0156879	0.0316051	−0.5	0.669	−0.1516738	0.1202981
_cons	−3.939082	7.507129	−0.52	0.652	−36.23965	28.36149

TABLE 6 | Subgroup analysis of working memory issues in AD patients.

Group	Subgroup	*N*	SMD	95% CI	*p*	I^2
Age	65–75	2	0.161	−0.084, 0.406	0.748	0.00%
	Older than 75	6	0.397	0.154, 0.641	0.265	22.40%
Intensity (%)	35–59	1	0.146	−0.229, 0.521	—	—
	60–79	5	0.408	0.126, 0.689	0.534	0.00%
	80–89	2	0.233	−0.036, 0.502	0.051	73.70%
Frequency (times/week)	1–2 times/week	3	0.274	−0.003, 90.550	0.174	42.70%
	3–4 times/week	5	0.284	0.064, 0.505	0.303	17.50%
Time (min)	30≤min<60	1	0.137	−0.148, 0.423	–	–
	60≤min<90	5	0.404	0.139, 0.668	0.169	37.80%
	90≤min≤150	2	0.279	−0.098, 0.657	0.734	0.00%
Duration (week)	8–12 weeks	2	0.526	0.011, 1.041	0.144	53.10%
	16 weeks	3	0.282	0.030, 0.535	0.303	16.10%
	24–48 weeks	3	0.212	−0.054, 0.478	0.837	0.00%
Event	Dual-task exercises	3	0.491	−0.014, 0.995	0.165	46.7%
	Multimodal exercise	5	0.396	0.012, 0.780	0.038	60.7%

CI −0.2011265 to 0.2131423, $p = 0.912$), frequency (95% CI −1.843857 to 1.376603, $p = 0.596$), time (95% CI −0.0309679 to 0.0251433, $p = 0.699$), or duration (95% CI −0.1516738 to 0.1202981, $p = 0.669$).

All eligible studies were analyzed in subgroups based on age, intensity, frequency, time, and duration, as shown in **Table 6**. The results from subgroup analysis are as follows: (1) age: physical activity was beneficial for AD patients aged 65–75 years with working memory issues. (2) Intensity: for working memory issues in AD patients, maintaining a 60–79% MHR during physical activity was more effective. (3) Frequency: the frequency of physical activity has a significant impact on the improvement of the working memory issues in AD patients, and the effect of 3–4 times/week was better than the effect of 1–2 times/week. (4) Time: a total of 60–150 min per exercise session significantly improved working memory in AD patients. (5) Duration: an intervention duration of 16 or 24–48 weeks showed a significant effect on working memory issues in AD patients. (6) Event: for working memory issues in AD patients, dual-task exercises had a significant effect.

Effect of Physical Activity on Cognitive Flexibility Issues in AD Patients

Nine articles (Vreugdenhill et al., 2012; Andrade et al., 2013; Holthoff et al., 2015; Hoffmanna et al., 2016; Ohman et al., 2016; Pedroso et al., 2017; Tootsa et al., 2017; Vidoni et al., 2017; Silvaa et al., 2019) evaluated the effects of physical activity on cognitive flexibility issues in AD patients. An asymmetrical funnel plot was presented. According to the funnel plot, there were two outliers (**Figure 6**). There was a moderate heterogeneity in the research literature ($p = 0.025$, $I^2 = 54.5\%$), and the meta-analysis was performed using a random-effects models (**Figure 7**). **Figure 7** shows that the meta-analysis of nine studies demonstrated that physical activity had a significant effect on improving cognitive flexibility in AD patients (SMD = 0.23, 95% CI −0.02 to 0.47, $p < 0.01$).

The analysis of heterogeneity and sensitivity showed that there was considerable bias in the studies by Vreugdenhill et al. (2012) and Holthoff et al. (2015). Therefore, a meta-analysis of the remaining RCTs was performed after exclusion. The results showed that the heterogeneity was reduced ($I^2 = 7.4\%$, $p = 0.372$, SMD = 0.06, 95% CI −0.11, 0.23), and that the differences between groups were significant ($p < 0.01$).

The results of the regression of covariates for working memory issues in AD patients are presented in **Table 7**. For working memory, there were no significant effects of age (95% CI −0.2086577 to 0.2332289, $p = 0.608$), intensity (95% CI −0.2536149 to 0.2638656, $p = 0.843$), frequency (95% CI −5.644876 to 5.888054, $p = 0.833$), time (95% CI −0.0894664

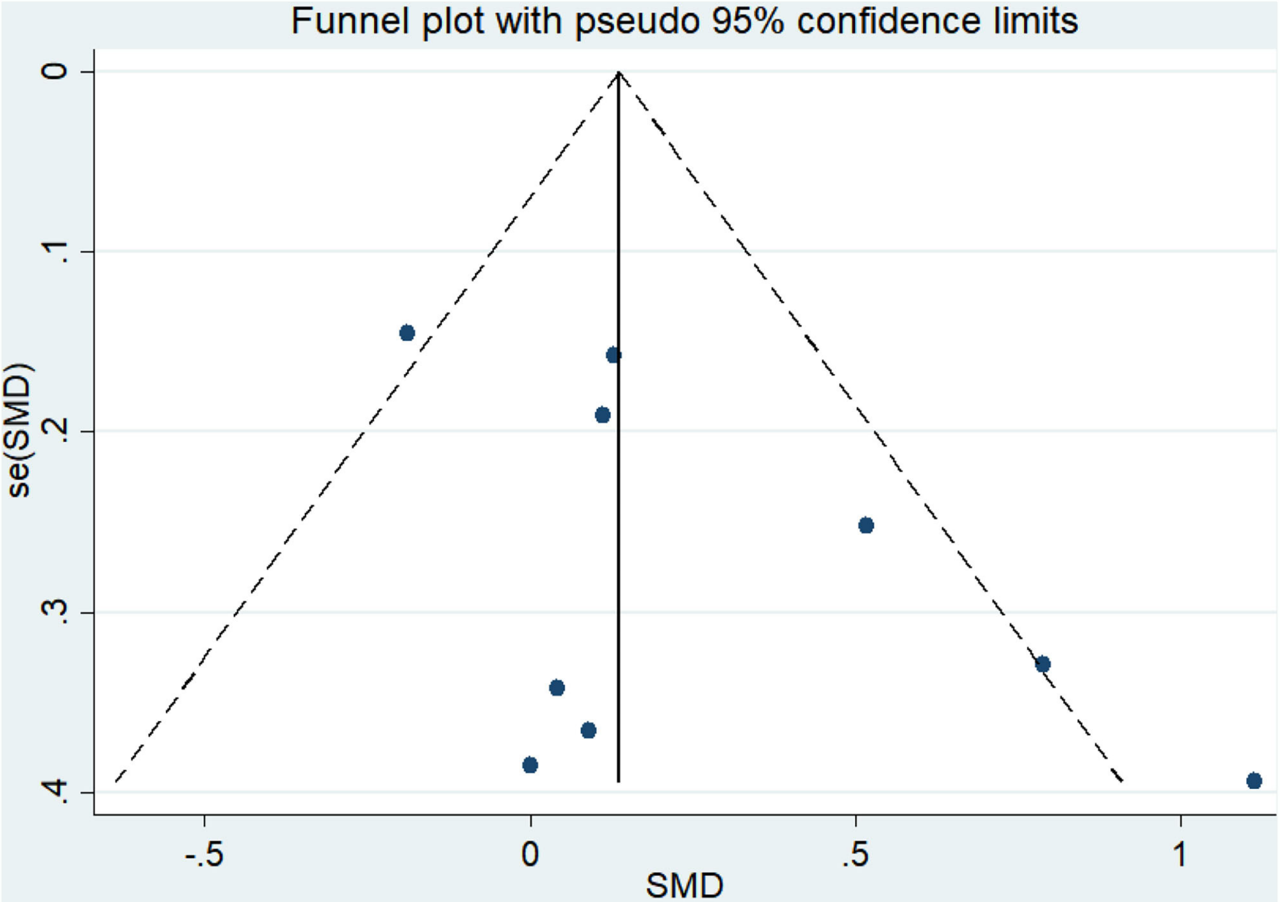

FIGURE 6 | Funnel plot of publication bias for cognitive flexibility.

to 0.1045166, $p = 0.505$), or duration (95% CI −0.2578807 to 0.2722502, $p = 0.789$).

The results from the subgroup analysis are as follows (**Table 8**): (1) age: physical activity was beneficial for cognitive flexibility issues in AD patients who were older than 75 years. (2) Intensity: for cognitive flexibility issues in AD patients, the effect of maintaining a 60–79 or 80–89% MHR was more effective. (3) Frequency: for cognitive flexibility issues in AD patients, the effect of performing physical activity 1–2 or 3–4 times/week was more effective. (4) Time: a total of 60–90 min per exercise session significantly improved cognitive flexibility in AD patients. (5) Duration: an intervention duration of 16 or 24–48 weeks showed a significant effect on cognitive flexibility issues in AD patients. (6) Event: for cognitive flexibility issues in AD patients, both dual-task exercises and multimodal exercise had significant effects.

Effect of Physical Activity on ADL Issues in AD Patients

Ten articles (Venturelli et al., 2011; Vreugdenhill et al., 2012; Chang et al., 2015; Holthoff et al., 2015; El-Kader and Al-Jiffr, 2016; Hoffmanna et al., 2016; Pedroso et al., 2017; Rolland et al., 2017; Vidoni et al., 2017; Fonte et al., 2019) evaluated the effects of physical activity on ADL issues in AD patients. An asymmetrical funnel plot was presented. Funnel plot indicated that there were three outliers (**Figure 8**). Heterogeneity testing of the study literature showed high heterogeneity ($p < 0.000$, $I^2 = 86.4\%$), and a random-effects model was used for the meta-analysis (**Figure 9**). **Figure 9** shows that the meta-analysis of 10 studies demonstrated that physical activity had significant effects on improving ADLs in AD patients (SMD = 0.68, 95% CI 0.19–1.16, $p < 0.001$).

The analysis of heterogeneity and sensitivity showed that there was considerable bias in the studies by Venturelli et al. (2011), Holthoff et al. (2015), and El-Kader and Al-Jiffr (2016) thus, a meta-analysis of the remaining RCTs was performed after exclusion. The results showed that the heterogeneity was reduced ($I^2 = 45.1\%$, $p = 0.091$, SMD = 0.15, 95% CI −0.10, 0.39), and that the differences between groups were significant ($p < 0.001$).

The results of the regression of covariates for ADL issues in AD patients are presented in **Table 9**. For ADLs, there were no significant effects of age (95% CI −0.2683096 to 0.4846618, $p = 0.47$), intensity (95% CI −0.2702262 to 0.0794482, $p = 0.204$),

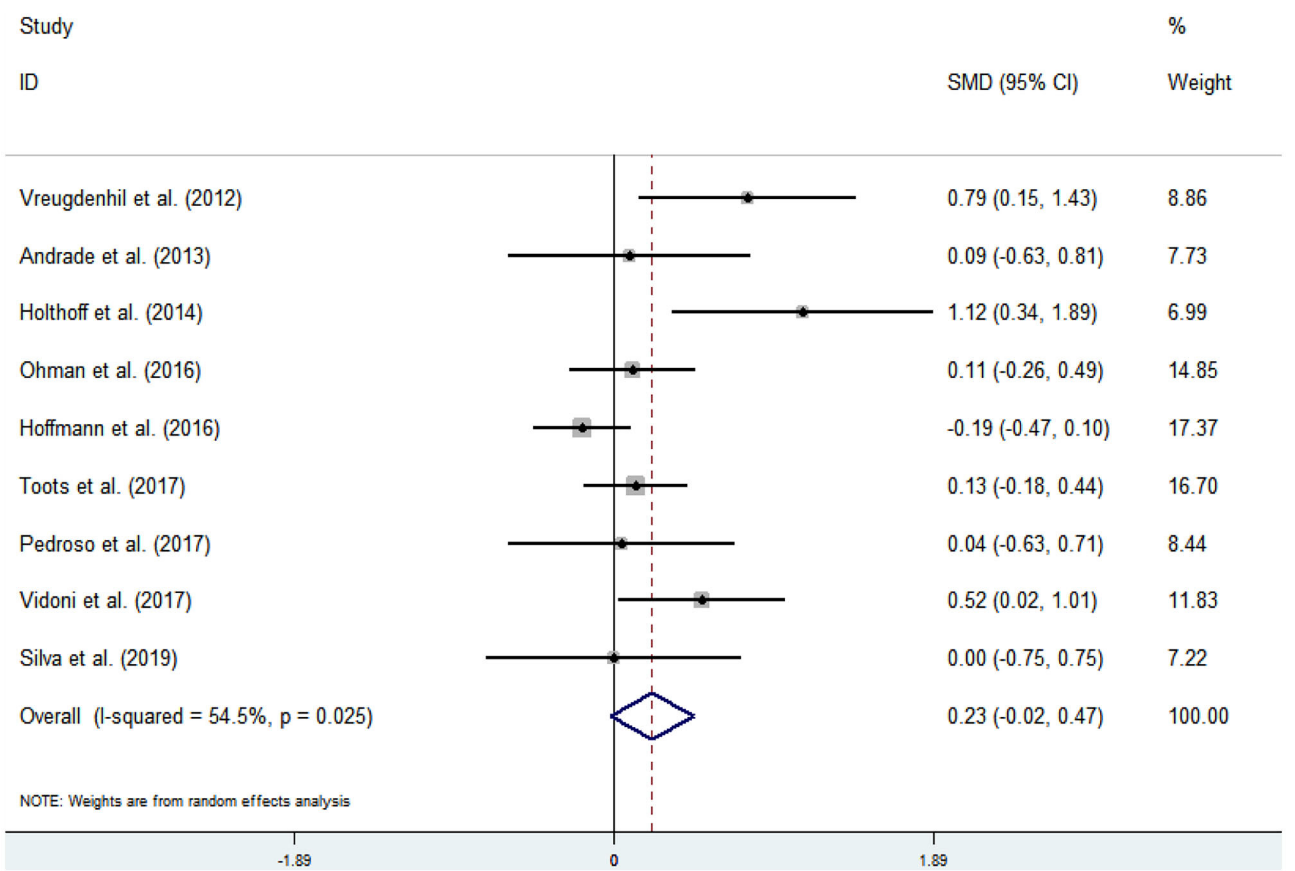

FIGURE 7 | Effect of physical activity on cognitive flexibility.

frequency (95% CI −1.392111 to 1.053637, $p = 0.72$), time (95% CI −0.0623979 to 0.035701, $p = 0.492$), or duration (95% CI −0.2969797 to 0.113052, $p = 0.281$).

The results from the subgroup analysis are as follows (**Table 10**): (1) age: physical activity was beneficial for ADL issues in AD patients who were older than 75 years. (2) Intensity: for ADL issues in AD patients, the effect of maintaining a 60–79% MHR was more effective. (3) Frequency: for ADL issues in AD patients, the effect of performing physical activity 3–4 times/week was more effective. (4) Time: a total of 30–60 or 60–90 min per exercise session significantly improved the ADL issues in AD patients. (5) Duration: for ADL issues in AD patients, the intervention duration was not important. (6) Event: for ADL issues in AD patients, multimodal exercise was significant.

DISCUSSION

The purpose of this systematic review and meta-analysis was to compile and analyze the literature pertaining to RCTs on physical activity (e.g., aerobic exercise, aerobic fitness, walking, cycling, strength training, balance training, and flexibility training) in relation to its influence on executive function, working memory, cognitive flexibility, and ADLs among AD patients to determine an optimal exercise prescription. The results suggest that physical activity can improve executive function, working memory, cognitive flexibility, and ADL issues in AD patients.

This systematic review investigated the influence of physical activity on executive function and ADL issues in AD patients. Research suggests that the effect size of executive function was 0.22–0.62 ($p < 0.05$), that of working memory was 0.11–0.45 ($p < 0.05$), that of cognitive flexibility was −0.02 to 0.47 ($p < 0.01$), and that of ADLs was 0.19–1.16 ($p < 0.001$). Furthermore, significant heterogeneity may have been present in the study by Holthoff et al. (2015). In this study, physical activity was conducted on comfortable chairs to encourage patients to participate and prevent falls and other injuries. This method was different from those used in other studies and may be the cause of the heterogeneity.

The subgroup analysis showed that, for executive function issues, performing moderate-to-high-intensity dual-task exercises or multimodal exercise for more than 60 min per session for 16 weeks had a greater effect on AD patients. Regarding frequency, performing physical activity 1–2 times/week was

TABLE 7 | Covariate regression analysis of cognitive flexibility issues in AD patients.

_ES	Coef.	Std. err.	*t*	*p* > *t*	(95% CI)	
Age	0.0122856	0.0173886	0.71	0.608	−0.2086577	0.2332289
Intensity (%)	0.0051253	0.0203633	0.25	0.843	−0.2536149	0.2638656
Frequency (times/week)	0.121589	0.4538306	0.27	0.833	−5.644876	5.888054
Time (min)	0.0075251	0.0076334	0.99	0.505	−0.0894664	0.1045166
Duration (week)	0.0071848	0.0208611	0.34	0.789	−0.2578807	0.2722502
_cons	−2.169054	2.459361	0.88	0.540	−33.4182	29.08009

TABLE 8 | Subgroup analysis of cognitive flexibility issues in AD patients.

Group	Subgroup	*N*	SMD	95% CI	*p*	I^2
Age	65–75	2	−0.011	−0.258, 0.237	0.015	83.00%
	Older than 75	5	0.103	−0.104, 0.309	0.998	0.00%
Intensity (%)	35–59	1	0.112	−0.263, 0.487	–	–
	60–79	3	0.29	−0.058, 0.638	0.441	0.00%
	80–89	3	−0.039	−0.241, 0.163	0.336	8.30%
Frequency (times/week)	1–2 times/week	3	0.225	−0.053, 0.503	0.36	2.20%
	3–4 times/week	4	−0.025	−0.218, 0.168	0.506	0.00%
Time (min)	30≤ min <60	2	−0.042	−0.252, 0.168	0.141	53.90%
	60≤ min <90	4	0.082	−0.195, 0.359	0.994	0.00%
	90≤ min ≤150	1	0.518	0.024, 1.013	–	–
Duration (week)	8–12 weeks	2	0.424	−0.477, 0.525	0.174	56.80%
	16 weeks	3	−0.031	−0.233, 0.170	0.318	12.70%
	24–48 weeks	2	0.260	−0.039, 0.559	0.199	39.40%
Event	Dual-task exercises	2	0.107	−0.225, 0.440	0.960	0.00%
	Multimodal exercise	5	0.073	−0.175, 0.322	0.174	37.1%

found to be significant. In addition, for working memory and cognitive flexibility issues, performing 60–90 min of moderate-intensity dual-task exercises 1–4 times/week was more effective. The subgroup analysis indicated that, for ADL issues, maintaining a 60–79% MHR during multimodal exercise 3–4 times/week for 30–90 min each time had a greater effect on AD patients. In addition, in the subgroup analyses of executive function, working memory, cognitive flexibility, and ADL issues, maintaining a 35–59% MHR during physical activity did not show a strong effect compared with maintaining a 60–79 or an 80–89% MHR. Performing physical activity 1–4 times/week for 60–90 min per exercise session significantly improved executive function, working memory, cognitive flexibility, and ADL issues in AD patients. In addition, this meta-analysis provides evidence to support the inclusion of aerobic training and strength, flexibility, balance, and other physical activities to improve executive function and ADL issues in AD patients. For AD patients with executive function, working memory, cognitive flexibility, and ADL issues, both dual-task exercises and multimodal exercises had significant effects. Notably, for working memory and cognitive flexibility issues, dual-task exercises showed a strong influence compared with multimodal exercises. Coincidentally, our findings support the WHO recommendations (World Health Organization Physical Activity Older Adults, 2017). In addition, the characteristics of exercise intervention in the included studies support the frequency, intensity, and time per session recommended by the WHO, but slightly lower than the WHO recommendations based on expert advice. Our meta-analysis showed that the current WHO recommendations can be considered an effective exercise prescription for AD patients; however, future studies are needed to determine which combinations of intervention methods, intensity, duration of each intervention session, frequency, and duration best improve executive function and ADL issues among older adults diagnosed with AD.

Systematic reviews showed that physical activity can improve the attention, cognitive function, executive function, and language of AD patients (Coelho et al., 2009; Farina et al., 2014). These authors agree that there is not enough theoretical support for the ideal intervention program, and that there is no consensus on the intensity, frequency, and duration of exercise. However, long-term physical activity stimulates growth factors, neurotransmitter synthesis, oxygenation, and plasticity to produce nerve and neuroprotective effects on the brain (Deslandes et al., 2009). The beneficial effects of physical activity on brain aging or dementia have not been well-documented (Herholz et al., 2013). However, animal studies have revealed that the activation of adult neurogenesis (Kempermann et al., 2010) or the increase in plasma levels of neuroplasticity-related brain-derived neurotrophic factors (Coelho et al., 2014) is related to physical activity. Furthermore, some mechanisms related to physical activity help to improve

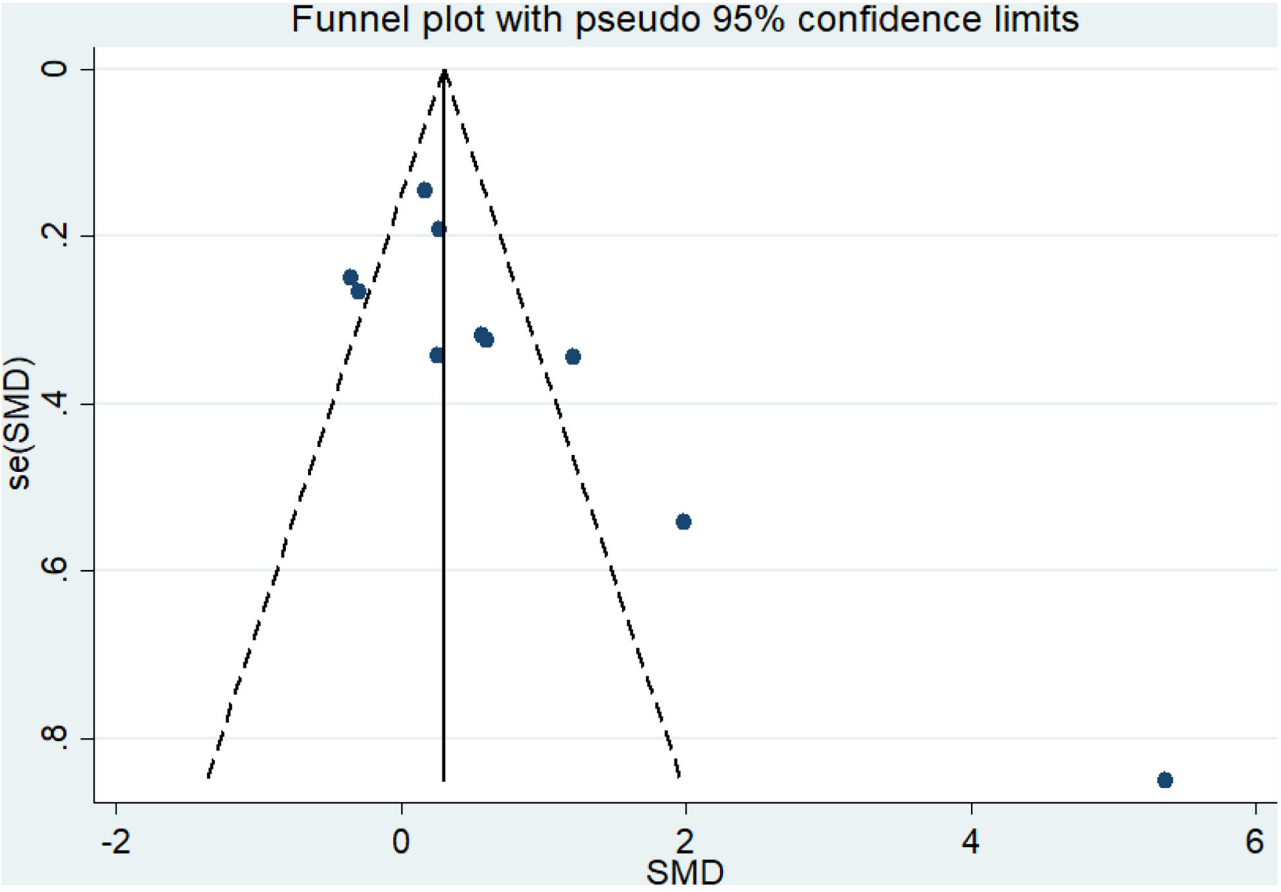

FIGURE 8 | Funnel plot of publication bias for ADLs.

cognitive function, such as improvement of the nervous system, including promoting the synthesis of neurotransmitters and improving cerebral blood flow (Eggermont et al., 2006; Lista and Sorrentin, 2009). Some studies have shown that physical activity can increase brain-derived neurotrophic factor and also have a positive impact on the brain neuroplasticity. Kramer and Erickson found that in rodents, physical activity induces increased levels of brain-derived neurotrophic factor in the frontal cortex, hippocampus, and cerebellum and promotes the formation of new capillaries in these areas (Kramer and Erickson, 2007). Some authors believe that physical activity improves cerebral circulation by increasing cerebral blood flow and oxygen supply (Hamer and Chid, 2009; Sofifi et al., 2011), while promoting cardiovascular and cerebrovascular health by lowering blood pressure and blood lipid levels. Physical activity also promotes inflammatory markers and can effectively enhance endothelial function (Kivipelto et al., 2005). Furthermore, physical activity can stimulate the proliferation of neurons in the hippocampus (Erickson et al., 2011). Therefore, the effect of physical activity on clinical performance in AD (e.g., cognitive and executive functions) may rely on improvement in brain functionality.

Previous studies have shown that physical activity can improve the cognitive and executive functions of the elderly with cognitive impairment (Scherder et al., 2005; Lautenschlager et al., 2008; Uffelen et al., 2008; Baker et al., 2010; Lam et al., 2011). The executive function is mainly responsible for the self-regulation of behavior and is the key cognitive resource, including the ability to initiate, plan, sequence, and monitor (Miyake and Friedma, 2012). In AD patients, executive dysfunction is a prominent clinical symptom that directly affects the patient's self-regulation of behavior and ADLs (Boyle et al., 2003; Razani et al., 2007).

The promoting effect of non-pharmacological treatment methods on the improvement of the condition of AD patients has been confirmed (Morley and Silve, 1995; Cohen-Mansfield and Mintze, 2005). Interventions, such as physical activity, have been shown to improve cognitive function and executive function and are even effective for frail residents of nursing homes (Lazowski et al., 1999). At the same time, exercise intervention may produce effective protective mechanisms to prevent the decline in the ADLs. At present, it has been confirmed that suitable physical activities can inhibit the pathophysiological changes of AD by regulating the expression and hydrolysis of amyloid precursor protein, reducing the production of β

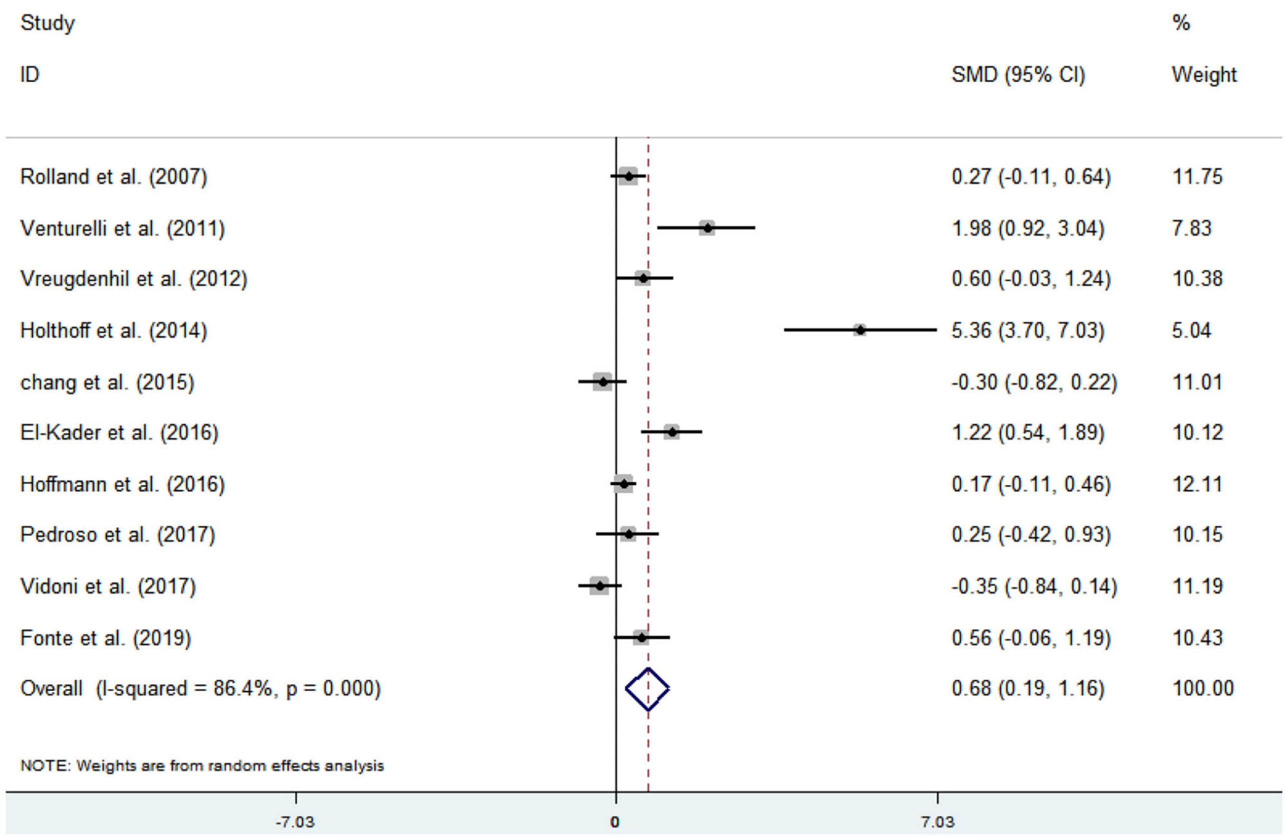

FIGURE 9 | Effect of physical activity on ADLs.

TABLE 9 | Covariate regression analysis of ADL issues in AD patients.

_ES	Coef.	Std. err.	*t*	*p > t*	(95% CI)	
Age	0.1081761	0.1355999	0.8	0.47	−0.2683096	0.4846618
Intensity (%)	−0.095389	0.0629716	−1.51	0.204	−0.2702262	0.0794482
Frequency (times/week)	−0.1692369	0.4404458	−0.38	0.72	−1.392111	1.053637
Time (min)	−0.0133484	0.0176663	−0.76	0.492	−0.0623979	0.035701
Duration (week)	−0.0919639	0.0738411	−1.25	0.281	−0.2969797	0.113052
_cons	2.195003	9.602787	0.23	0.83	−24.46661	28.85662

amyloid protein, and scavenging free radicals, among other actions (Radak et al., 2010; Foster et al., 2011). In addition, on the one hand, the decline of ADLs among AD patients is due to a decline in the cognitive level; on the other hand, it is closely related to the atrophy of muscles with the development of age and disease (Sakuma and Yamaguch, 2011). Physical activity is an important measure to combat skeletal muscle atrophy. It can increase the quality of skeletal muscle, output power of physical activity per unit time, and skeletal muscle endurance. According to the changes in muscle stimulation during physical activity, the number of activated transverse bridges can be increased, thereby enhancing muscle flexibility (Jin et al., 2020). Furthermore, the contraction ability of respiratory muscles is enhanced after exercise, which is conducive to the extension of patient's trunk and limbs, and provides opportunities for improving limb coordination and strengthening exercise ability (Liu et al., 2018). Therefore, physical activity can improve ADLs in AD patients by increasing the quality of skeletal muscle, enhancing muscle activity, improving limb coordination, and exercise performance, etc.

In this review, one article showed that there was no significant effect of physical activity on executive function among AD patients. Specifically, Morris et al. (2017) showed that there was no significant difference in the improvement of executive function between the intervention group and the control group. Aerobic exercise interventions were used in this study, which are different from other interventions. This may be one of the reasons for the lack of a significant difference. However, aerobic

TABLE 10 | Subgroup analysis of ADL issues in AD patients.

Group	Subgroup	*N*	SMD	95% CI	*p*	I^2
Age	65–75	4	0.019	−0.358, 0.395	0.049	61.90%
	Older than 75	3	0.328	0.038, 0.618	0.708	0.00%
Intensity (%)	35–59	2	−0.02	−0.623, 0.582	0.05	73.90%
	60–79	4	0.255	−0.189, 0.699	0.096	52.70%
	80–89	1	0.172	−0.114, 0.458	–	–
Frequency (times/week)	1–2 times/week	2	−0.02	−0.623, 0.582	0.05	73.90%
	3–4 times/week	4	0.147	−0.158, 0.451	0.203	34.90%
	5–7 times/week	1	0.603	−0.031, 1.238	–	–
Time (min)	30≤ min <60	4	0.291	−0.087, 0.668	0.225	32.20%
	60≤ min <90	2	0.18	−0.159, 0.519	0.179	38.80%
	90≤ min ≤150	1	−0.349	−0.839, 0.141	–	–
Duration (week)	8–12 weeks	1	0.253	−0.42, 0.926	–	–
	16 weeks	3	0.137	−0.281, 0.554	0.091	58.30%
	24–48 weeks	3	0.142	−0.347, 0.632	0.049	66.80%
Event	Single exercises	1	−0.298	−0.821, 0.224	–	–
	Multimodal exercise	6	0.210	−0.033, 0.453	0.165	36.3%

"–" heterogeneity test cannot be conducted due to the lack of literature.

exercise interventions were also used in the study by Vidoni et al. (2017), and the results showed a significantly different effect on ADL issues in AD patients. This result suggests that aerobic exercise may be more effective in improving the quality and activity of skeletal muscle in AD patients. In general, more RCTs are required to demonstrate the effect of aerobic exercise on executive function and ADL issues in AD patients. In addition, other studies have shown that physical activity can improve executive function and ADL issues in AD patients. Therefore, physical activity is feasible and may provide an alternative or adjuvant treatment for patients with mild to moderate or even late AD and their family nurses.

LIMITATIONS

There are some limitations and deficiencies in this study. The authenticity and reliability of the results are affected by the course of disease and the frequency, time, intensity, and duration of the intervention in AD patients. There are certain differences in the quality of the eligible articles for our study: (1) only four studies showed their concealed allocation, which may be one of the reasons for the systematic bias of results (PEDro-scale, 2010). (2) Only four articles referred to blinding of assessors. (3) Most of the studies lacked a description of the course of the disease, which could have led to a lack of understanding of the effectiveness of physical activity on executive function and ADL issues in AD patients. (4) Most studies did not mention the severity of disease among patients with AD, which made it impossible to provide patients with more targeted exercise prescriptions. (5) Only two authors, Hoffmanna et al. (2016) and Silvaa et al. (2019), mentioned the effect of physical activity on inhibitory functions in AD patients. Studies on inhibitory executive functions among AD patients are scarce and were not included in the meta-analysis for the time being to avoid errors. Furthermore, the differences in experimental intensity, time, frequency, duration, and outcome measure methods could have led to differences in outcomes and caused difficulty in explanations.

CONCLUSIONS

Research has proven that physical activity can effectively improve executive function, working memory, cognitive flexibility, and ADL issues in AD patients and may be an alternative or auxiliary treatment. In the future, it will necessary to provide more accurate neuropsychological evaluations of each executive function, working memory, cognitive flexibility, and ADL dimension and to grade the course of AD to obtain more accurate exercise prescriptions for physical activity interventions. In the absence of adverse reactions, medical profession could combine physical activity with daily medical treatment to optimize the treatment of executive function, working memory, cognitive flexibility, and performance of ADLs in AD patients. In addition, the conclusion of this study still needs to be confirmed by a high-quality large-sample RCT.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

LW and LZ contributed to the idea and structural design plan for review. XJ and HZ applied the search strategy. LZ, LW, and LL applied the selection criteria to screen out qualified documents. LW and XJ completed the deviation risk assessment. LZ wrote the manuscript.

LW, LL, and HZ edited the manuscript. All authors analyzed and interpreted the data. All authors have read the complete manuscript and reached a consensus on the manuscript version.

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SYSTEMATIC REVIEW
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Effects of Acute and Chronic Exercises on Executive Function in Children and Adolescents: A Systemic Review and Meta-Analysis

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Background: Physical exercises can affect executive function both acutely and chronically, with different mechanisms for each moment. Currently, only a few reviews have elaborated on the premise that different types of exercises have different mechanisms for improving executive function. Therefore, the primary purpose of our systematic review was to analyze the effects of acute and chronic exercises on executive function in children and adolescents.

Objective: We identified acute and chronic exercise studies and randomized controlled trials (RCTs) of executive function in children and adolescents that reported overall effect, heterogeneity, and publication bias of acute and chronic exercises on executive function.

Methods: We searched for RCTs of exercise interventions in children and adolescents from databases including PubMed, Web of Science, Scopus, The Cochrane Library, CNKI (China National Knowledge Infrastructure), and Wanfang, from January 1 2009 to December 31 2019. We performed methodological quality evaluations on the included literature using the Physiotherapy Evidence Database Scale (PEDro) and graded evidence with a meta-analysis using Stata 12.0 software.

Results: In total, 36 RCTs were included (14 acute exercises, 22 chronic exercises); the overall results of the meta-analysis (4,577 students) indicated that acute exercises significantly improved working memory (standardized mean difference (SMD) = −0.72; 95% confidence interval (CI) −0.89 to −0.56; $p < 0.001$), inhibitory control (SMD = −0.25; 95% CI −0.40 to −0.09; $p = 0.002$), and cognitive flexibility (SMD = −0.34; 95% CI −0.55 to −0.14; $p < 0.005$), whereas chronic exercises significantly improved working memory (SMD = −0.54; 95% CI −0.74 to −0.33; $p < 0.001$), inhibitory control (SMD = −0.30; 95% CI −0.38 to −0.22; $p < 0.001$), and cognitive flexibility (SMD = −0.34, 95 % CI −0.48 to −0.20, $p < 0.001$).

Conclusion: Acute and chronic exercises can effectively improve the executive function of children and adolescents. The effects on inhibitory control and cognitive flexibility are considered as small effect sizes, while the effects on working memory are considered as moderate effect size. Limited by the quantity and quality of the included studies, the above conclusions need to be verified with more high-quality studies.

Keywords: executive function, acute exercise, chronic exercise, cognitive, adolescents

INTRODUCTION

A sedentary lifestyle and physical inactivity (insufficient exercises time) are prevalent among children and adolescents (Sisson et al., 2009; Qi et al., 2019) and are negatively linked with their physical and psycho-cognitive health (Tremblay et al., 2011; Flashner et al., 2019). Specifically, these unhealthy lifestyle behaviors result in obesity (Rey-Lopez, 2008), uncoordinated movements (Ferguson et al., 2014; Flashner et al., 2019; Kong et al., 2019; Riquelme et al., 2019), negative emotions (depression, anxiety, suicide attempts) (Berardelli et al., 2018; Thivel et al., 2018; Padulo et al., 2019) and a severe deficit of cognitive functions (Torrens-Burton et al., 2017; Koolhaas et al., 2019; Loprinzi et al., 2019). Among the components of cognitive functioning, inhibitory control, working memory, and cognitive flexibility play a critical role in the development of school-age children and their educational achievement or academic performance (Best, 2010; Willoughby et al., 2012).

Diamond proposed a three-factor model of executive functions and stated that inhibitory control, working memory, and cognitive flexibility are the three core executive functions (EF); the three aforementioned cognitive abilities work together to influence higher-order executive functions such as reasoning, planning, and problem solving (Diamond, 2013). However, there is little longitudinal experimental evidence in the field of sports and health promotion to prove that physical activity is relevant to high-level executive functions such as decision-making and reasoning in children and adolescents. In contrast, the more such evidence appears in the context of techniques and tactics in high-level athletes (Taddei et al., 2012; Bjoern et al., 2018; Beavan et al., 2020). Therefore, this review only considers the three main executive functions of inhibitory control, working memory, and cognitive flexibility. Firstly, inhibitory control (self-control) refers to the ability to suppress irrelevant reactions, allowing children to control automatic or impulsive behaviors while performing minimal automatic reactions (Pindus et al., 2019); secondly, working memory (refreshing tasks) allows children to register information in the brain and then to perform cognitive operations on it (Keita et al., 2011); thirdly, cognitive flexibility (tasks of conversion) refers to the ability of a child to move flexibly to a new situation or another state (Masley et al., 2009). When EF are impaired, children generally show abnormalities in social functions, emotions, and cognition (Goodall et al., 2018; Wang et al., 2019), often accompanied by learning difficulties, conduct disorders, and maladaptive phenomena (Rocha et al., 2019). Thus, such cognitive abilities in the growth and development stage are undoubtedly crucial for children and adolescents.

Emerging evidence indicates that physical activity and exercise can influence executive functions such as inhibitory control, working memory and cognitive flexibility both acutely and chronically (Rathore and Lom, 2017; De Greeff et al., 2018; Vazou et al., 2019). Furthermore, chronic exercises as a part of healthy lifestyle behaviors are widely recognized to be associated with improved EF across different age groups (Hillman et al., 2011; Li et al., 2017), while the expanding topic on acute exercises (referring to a single bout of exercises taking 10–60 min) indicates their potential to improve these cognitive outcomes (Byun et al., 2014). However, to date, very few reviews have systematically and simultaneously evaluated the effects of both exercise types on the three key EF components in children and adolescents; the reviews on this topic either focused on healthy adults and older adults (Ludyga et al., 2016; McSween et al., 2019; Chen et al., 2020) or chronic exercises alone in the same age group (Ludyga et al., 2016; Xue et al., 2019), or presented unclear information on a selected outcome (reaction time, accuracy, or derived scores) (Li et al., 2017; De Greeff et al., 2018; Sember et al., 2020). Meanwhile, previous studies have shown that physical activity is more sensitive to reaction time than the three key cognitive components (Ellemberg and St-Louis-Deschênes, 2010; Zhu, 2015). Against this background, the primary purpose of this review was to comprehensively analyze the effects of acute and chronic exercises on the EF of children and adolescents and to further explore the effects of acute and chronic exercises on the three different tasks of inhibitory control, working memory, and cognitive flexibility. In response to these differences in the literature, this review highlighted the relationship between exercises and EF, regulated by factors such as exercise type, exercise intensity, exercise duration, individual factors, and subcomponents of executive function.

METHOD

Our research follows the requirements of the international meta-analysis writing guidelines (the PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health-care interventions: explanation and elaboration) for selecting and utilizing research methods (Shamseer et al., 2015).

Retrieval Strategy

The databases PubMed, Web of Science, Scopus, The Cochrane Library, China National Knowledge Infrastructure (CNKI), and

Wan Fang were searched from January 1 2009 to December 31 2019. Two reviewers independently searched articles published in Chinese and English, supplemented by a manual search, and retrospectively included references if necessary. The following two sets of search terms were used: "physical activity" or "exercises" or "physical fitness" or "physical endurance" or "motor activity" or "physical education" or "sport" or "basketball" or "football" or "running" or "cycling" or "jumping" or "dancing" or "tai chi" or "yoga" or "aerobic" and "executive function" or "inhibition" or "inhibiting ability" or "self-control" or "working memory" or "updating" or "refreshing" or "cognitive flexibility" or "task-switching" or "shifting" and "child" or "student" or "toddler" or "preschooler" or "adolescents." If an article was incomplete or unavailable, we contacted the corresponding author by email to obtain detailed information. For literature tracing, based on the retrieved literatures or related references listed in the review, we used Baidu Scholar and Google Scholar to search for them retrospectively.

Inclusion Criteria and Exclusion Criteria

Two reviewers independently screened the articles. When there was a disagreement between the two reviewers, a third reviewer evaluated the original study to reach a consensus. Any potentially relevant research needed to meet the following inclusion criteria: (1) children and adolescent participants aged 5–18 years with right-hand dominance, corrected or normal vision and a healthy body were deemed eligible; (2) the exercise group was the primary intervention measure (e.g., aerobic-based, motor skill-based, combining aerobic, muscular activity, yoga, basketball), compared with different types of control groups (i.e., no-intervention control group, waiting list, and routine care) and all the intervention measures were motor skill-based or aerobic-based and clearly defined in terms of the exercise protocol; (3) preliminary studies were randomized controlled trials, and the randomization was done either on an individual or on a group (e.g., classroom) basis; (4) outcome indicators included test data on executive function (working memory, inhibition and cognitive flexibility), with a minimum of one outcome with quantitative data for calculating the pooled effect size. Conditions for exclusion from the study included: (1) ambiguous explanations of exercises interventions; (2) irrelevant outcomes; and (3) studies for which the full text could not be obtained.

Data Extraction

Two reviewers independently extracted data according to a predefined protocol. If there were any differences or inconsistencies, they would discuss the study with a third reviewer. They gathered the following information: (1) literature information, including author name, year of publication and country; (2) sample size (male sample); (3) socioeconomic status; (4) age of subjects, mainly used to divide the type of population; (5) intensity of exercise intervention, duration of intervention, time of intervention, frequency of intervention; (6) intervention program; (7) measurements, mainly including the three dimensions of working memory, inhibition and cognitive flexibility; and (8) adverse events and follow-up.

The Methodological Quality of the Included Studies

Similar to previous studies (Zou et al., 2018, 2019), the Physiotherapy Evidence Database Scale (PEDro) was used to assess the risk of bias (Macedo et al., 2010). The assessment tool includes 10 items, as follows: eligibility criteria, randomization, concealed allocation, similar baseline, assessor blindness, subject blindness, point estimation, comparison between groups, a retention rate of 85% or above and completeness of measurement results. Notably, the use of a blinded instructor was unrealistic during exercise interventions, and so this item was not considered. A higher total score (0–10 points) represents a better methodological quality, where a PEDro score $\geq$6 is categorized as the high-quality group while a PEDro score <6 is categorized into the low-quality group (Maher et al., 2003). The methodological quality of the included studies was independently assessed by two panelists using PEDro, and any differences were resolved by a third reviewer.

Statistical Analysis

Stata 12.0 (Stata Corp, College Station, TX) was used as data processing software (Press, 2009). We used the standardized mean difference (SMD) with a 95% confidence interval (CI) to analyze the combined effect size. According to the Cochrane systematic review manual, if a study included more than one control group, the sample size of the exercise intervention should be equally assigned during pair comparison in order to avoid analysis unit errors (Handoll et al., 2002). If statistical heterogeneity was found across studies ($I^2 \geq 50\%$, $p < 0.10$), we applied the random-effects model—otherwise, the fixed-effect model was applied—and we used the Hedges' g method to reflect the magnitude of exercise intervention (Liu et al., 2019). According to the criteria for evaluating effect volumes, a small effect was between $\geq$0.2 and <0.5, a medium effect was between $\geq$0.5 and <0.8, and a large effect was $\geq$0.8 (Hanley et al., 2003). The heterogeneity of the included studies was determined with the p-value (threshold point of 0.1) and I^2 statistics (25, 50, and 75%, representing small, medium, and large heterogeneity, respectively) (Liu et al., 2019).

Given that overall effect sizes may be influenced by heterogeneity factors (age, study quality, motor skill type, composite type, intervention duration, intervention frequency, and intervention time), several regression analyses were separately performed. Additionally, subgroup analyses were also performed for age, study quality, motor-skill type, composite type, and intervention duration, frequency, and time: (1) prepubertal children (5–12 years) vs. adolescents (12–18 years) (Cardoso, 2007); (2) PEDro scores of >6 points (high-quality studies) vs. PEDro scores of <6 (low-quality studies) (Maher et al., 2003); (3) open-skilled exercises (different types of motor skills that respond to individual requirements in a dynamically changing or unpredictable external environment, where physical education, basketball, and ping-pong belong to open exercises) vs. closed-skill exercises (movements with relatively stable sports environments, such as yoga and running) (Liu et al., 2019); (4) sole-mode training (the use of a single skill) vs. multimodal training (the use of a variety of skills including yoga and running, aerobic exercises); (5) 12 weeks was used as a cutoff for chronic exercise intervention; (6) intervention time referred to the timing of intervention, where a threshold of 30 min for chronic exercise was recommended; and (7) three times a week was used as a threshold for chronic exercise intervention frequency. The selection of these moderators was principally inspired by McMinn and Rathore (Mcminn, 2012; Rathore and Lom, 2017).

Evidence Certainty Assessment

The Grading Recommendations to Assess Development and Evaluation system (GRADE) is an evidence evaluation system and is one of the international standards for evidence quality and the classification of recommendation strength (Zhang et al., 2019). We evaluated the quality of the evidence for each outcome using the GRADE classification with four possible levels: I (high), where the real effect is similar to a credible estimate; II (moderate), where the true effect is closest to the estimated effect; III (low), where the actual effect may be significantly different from the estimated effect; and IV (very low), where the actual effect is likely to be significantly different from the estimated effect. Five factors can cause the quality of the evidence to decrease: (1) risk of bias; (2) imprecision; (3) inconsistency; (4) indirectness; and (5) publication bias.

RESULTS

Literature Search Results

The latest review of electronic searches (as of December 2019) retrieved a total of 455 articles. During the preliminary screening, we excluded 353 studies based on their title and abstract for reasons including duplications ($n = 95$), language ($n = 6$), or not being related to the subject content ($n = 252$). Further screening was performed by reading the full text, and 66 records were excluded because of non-randomized controlled trials ($n = 22$), no reported data for analysis ($n = 21$), review ($n = 3$), no major exercise interventions ($n = 13$), or non-healthy participants ($n = 7$). Finally, the meta-analysis included 36 articles: 14 for acute exercises and 22 for chronic exercises (**Figure 1**).

Eligible Research Features

The 36 articles included were randomized controlled trials (14 acute exercises, 22 chronic exercises), including 4,577 healthy participants (1,308 participants of acute exercises), of which 2,227 were in the experimental group (670 participants of

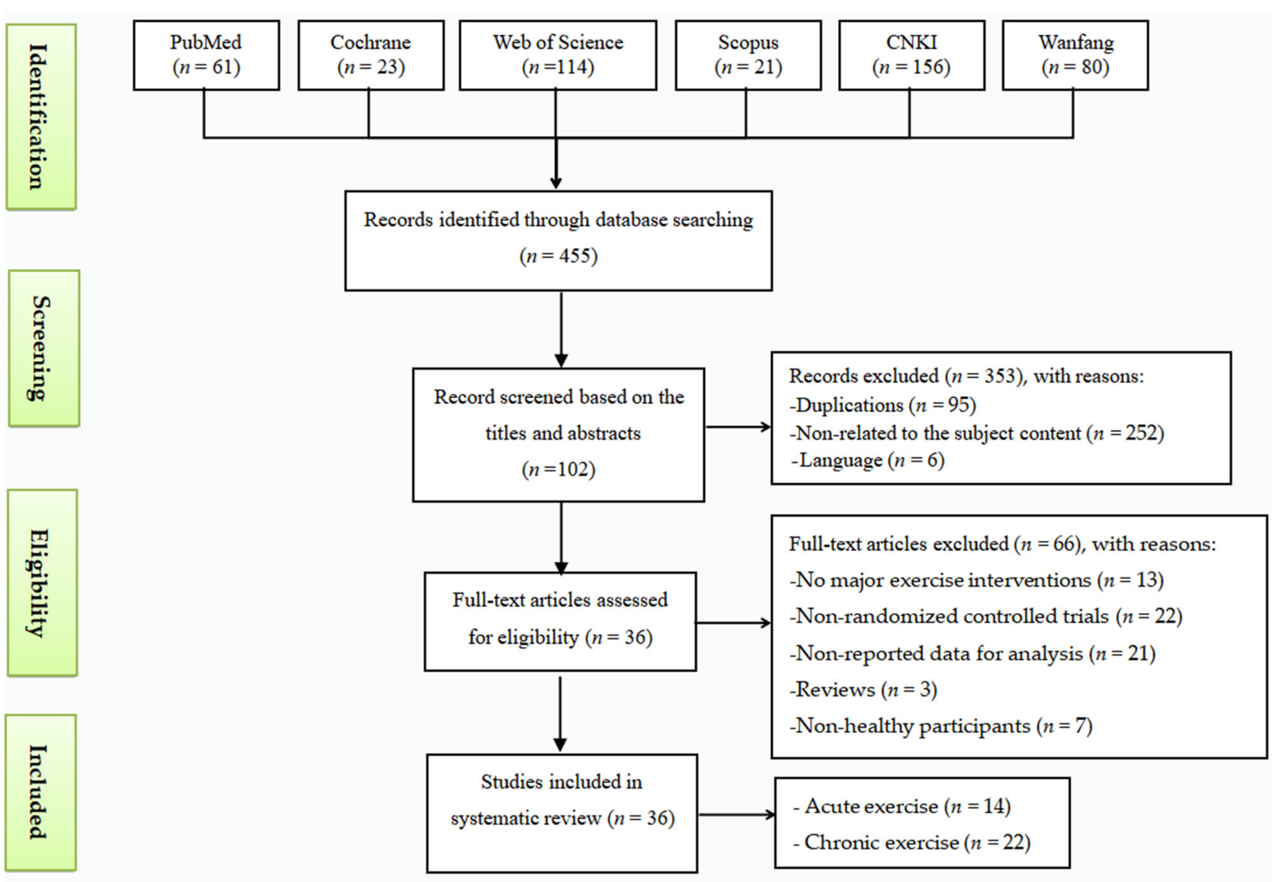

FIGURE 1 | Flow of the study selection method.

acute exercises) and 2,350 were in the control group (635 participants of acute exercises) (**Tables 1**, **2**). In acute exercises and chronic exercises, the ages of the included students ranged from 5 to 18 years old, while three of the studied articles did not specify age (Chaddock-Heyman et al., 2013; Weng et al., 2014; Budde et al., 2016). In terms of interventions, 12 studies used acute exercises—short-term, medium-intensity aerobic exercises, such as jogging or power cycling, with an exercise time from 10 to 40 min—and 20 studies used chronic exercise interventions with a duration from 8 to 20 weeks, 2–5 times a week, and with 30–90 min per session. Furthermore, each study consisted of at least one dimension of the outcome indicators of inhibitory control (10 acute exercises, 15 chronic exercises), working memory (nine acute exercises, 13 chronic exercises), and cognitive flexibility (three acute exercises, eight chronic exercises) in three dimensions. In addition, only three articles in the included studies reported follow-up status (Fisher et al., 2011; Telles et al., 2013; Tarp et al., 2016), and no adverse events occurred.

Methodological Quality Evaluation

The methodological quality of the included studies is presented in **Table 3**. The mean scores for acute and chronic exercise types were 7 and 6.77, respectively, indicating a high degree of credibility. All 36 studies were randomized controlled trials, five articles described the method for hiding random allocation (Kubesch et al., 2009; Ellemberg and St-Louis-Deschênes, 2010; Telles et al., 2013; Hillman et al., 2014; Budde et al., 2016), and the rest only mentioned random allocation. Eight studies adopted the blind-reviewer method (Fisher et al., 2011; Telles et al., 2013; Hillman et al., 2014; Chun et al., 2015; Jager et al., 2015; Budde et al., 2016; Chen et al., 2016; Yin et al., 2018), and five articles used the blind-examiner method (Fisher et al., 2011; Telles et al., 2013; Yan et al., 2014; Jager et al., 2015; Chen et al., 2016); the rest were implemented without a blind method. There were 11 articles that did not describe the source of their examination.

META-ANALYSIS RESULTS

Twenty-three studies examined the effect of exercises on inhibitory control (as measured by the Stroop, Go/no-go, or Flanker tasks). The aggregated result showed a significant benefit in favor of acute exercises on the inhibitory control of children and adolescents (SMD = −0.25; 95% CI −0.40 to −0.09, $I^2 = 9.9\%$, $p = 0.002$) (**Figure 2**). The aggregated result showed that chronic exercises can significantly shorten response times (SMD = −0.30; 95% CI −0.38 to −0.22, $I^2 = 64.2\%$, $p < 0.001$) (**Figure 3**). The SMDs of acute and chronic exercises were considered as small ESs.

Twenty-two studies (27 pairwise comparisons) examined the effect of exercises on working memory (as measured by digit span backward, Tower of London, and N-back tasks). A higher negative value of the mean change score for the reaction time

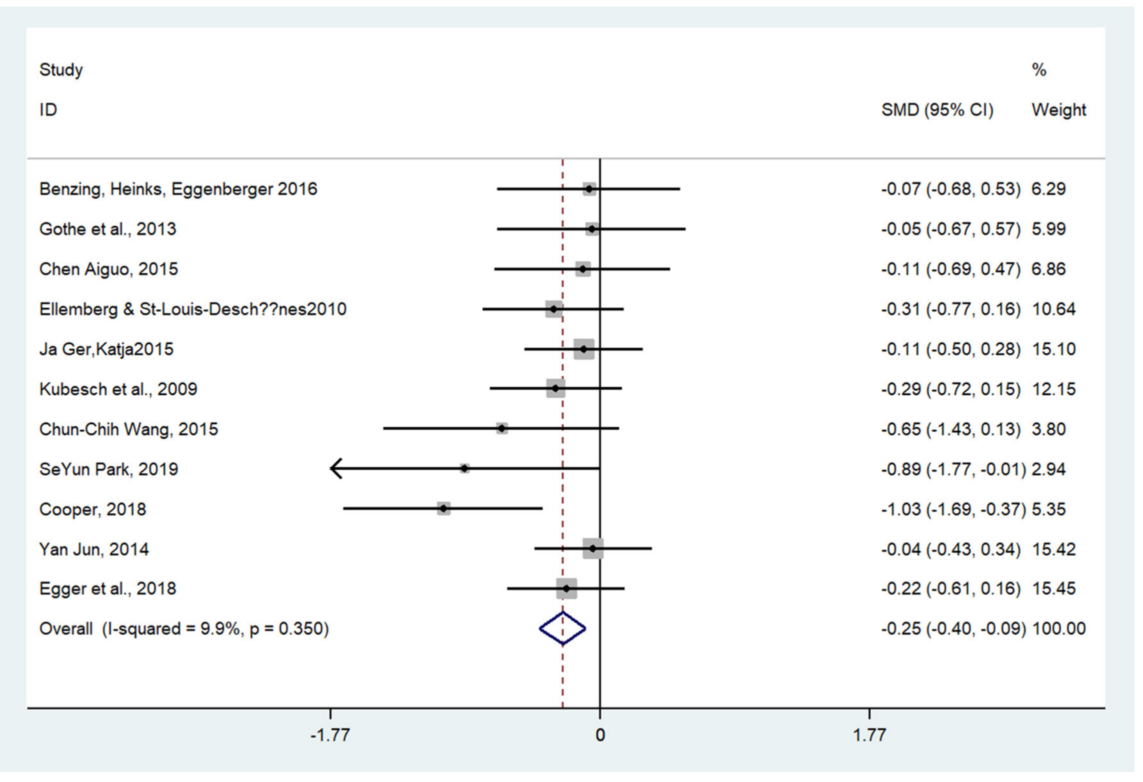

FIGURE 2 | The effect of acute exercises on inhibitory control (SMD = standardized mean difference; CI = confidence interval).

TABLE 1 | Characteristics of the studies included in the meta-analysis (acute exercises).

References	Location (Language)	Participant characteristics			Intervention program	Intervention characteristics		Outcome measured	Adverse event; Follow-up
		N (male)	SES	Mean age or Age range		Time (min)	Motion intensity		
Benzing et al. (2016)	Bern, Switzerland (English)	65 (34)	NR	14.51 ± 1.08	EG: Run + jump + resistance exercises (aerobic-based) CG: Usual care	15	60%−70%	① (Inhibition) ② (Fluency) ③ (Cognitive flexibility)	No No
Pate (2015)	Carolina, USA (English)	96 (37)	NR	10.70 ± 0.60	EG: Better ideas through exercises (aerobic-based) CG: Usual care	10–20	NR	② (Digit Recall)	No No
Gothe et al. (2013)	Urbana, USA (English)	40 (20)	NR	9.50 ± 0.50	EG: Yoga (motor skill-based) CG: Usual care	20	60%−70%	① (Stroop Test)	No No
Chen et al. (2015)	Yangzhou, China (Chinese)	130 (53)	NR	9.40 ± 0.30	EG: Basketball (motor skill-based) CG: Usual care	15–30	65%	① (Flanker task) ② (1-back) ③ (More-odd shifting)	No No
Ellemberg and St-Louis-Deschênes (2010)	Montreal, Canada (English)	72 (38)	NR	7.75 ± 0.65	EG: Basketball (motor skill-based) CG: Usual care	40	63%	① (Flanker task)	No No
Jager et al. (2015)	Bern, Switzerland (English)	219 (112)	6.90 (1.56)	11.35 ± 0.65	EG: Run + bicycle (combining aerobic and muscular activity) CG: Usual care	30	70%	① Wisconsin Card Sorting Test	No No
Kubesch et al. (2009)	Ulm, Germany (English)	81 (NR)	NR	13–14	EG: Run + resistance exercises (aerobic-based) CG: Usual care	30	NR	① (Flanker task) ② (1-back)	No No
Chun et al. (2015)	Taiwan, China (English)	22 (9)	NR	15.42 ± 1.47	EG: Bicycle (aerobic-based) CG: Usual care	30	65%	① Wisconsin Card Sorting Test	No No
Budde et al. (2010)	Berlin, Germany (English)	60 (0)	NR	14.37 ± 0.53	EG: Run (aerobic-based) CG: Usual care	12	50%-85%	② Digit Span task	No No
Yan et al. (2014)	Yangzhou, China (Chinese)	244 (113)	NR	9.50 ± 0.30	EG: Run (aerobic-based) CG: Usual care	30	60%−69%	① (Go/no-go) ② (1-back) ③ (More-odd shifting)	No No
Cooper et al. (2018)	Nottingham, UK (English)	41 (NR)	NR	12.30 ± 0. 71	EG: Basketball (motor skill-based) CG: Usual care	60	60%−70%	① (Stroop test) ② (Sternberg paradigm)	No No
Park and Etnier (2019)	Daejeon, Korea (English)	22 (NR)	NR	15.90 ± 0. 29	EG: Better ideas through exercises (aerobic-based) CG: Usual care	20	60%−70%	① (Stroop Test)	No No
Egger et al. (2018)	Bern, Switzerland (English)	216 (110)	NR	7.94 ± 0. 44	EG: Better ideas through exercises (aerobic-based) CG: Usual care	20	NR	① (Stroop Test)	No No
Vera et al. (2018)	Netherlands, Amsterdam (English)	38 (12)	NR	12.30±0.60	EG: Bicycle (aerobic-based) CG: Usual care	20-30	40%−60%	② (N-back)	No No

NR = not reported; EG = experimental group; CG = control group; SES = socioeconomic status; ① represents inhibitory control; ② represents working memory; ③ represents cognitive flexibility.

TABLE 2 | Characteristics of the studies included in the meta-analysis (chronic exercises).

Reference	Location (language)	Participant characteristics			Intervention program	Intervention characteristics			Outcome measured	Adverse event; follow-up
		N (male)	SES	Mean age or age range		Time (min)	Frequency (weekly)	Duration (week)		
Chen et al. (2016)	Yangzhou, China (Chinese)	40 (20)	NR	11.36 ± 0.57	EG: Aerobic dance CG: Usual care	40	3	8	① (Flanker task) ② (1-back) ③ (More-odd shifting)	No No
De Greeff et al. (2016)	Groninge, Netherlands (English)	499 (216)	NR	8.20 ± 0.70	EG: Aerobic exercises CG: Usual care	20–30	3	22	① Wisconsin Card Sorting Test	No No
Kval et al. (2017)	Stavanger, Norway (English)	429 (NR)	NR	10–11	EG: Jump rope + running + strength training (combining aerobic and muscular activity) CG: Usual care	45	2	10	① (Stroop Test)	No No
Jiang (2015)	Beijing, China (Chinese)	61 (25)	NR	5.56 ± 0.35	EG: Football (motor skill-based) CG: Usual care	35	2	8	① (Flexible-Item Selection)	No No
Xin (2012)	Shandong, China (Chinese)	40 (20)	NR	9.10 ± 0.32	EG: Tennis (motor skill-based) CG: Usual care	40	5	16	① (Flanker task); ② (1-back) ③ (More-odd shifting)	No No
Budde et al. (2016)	Hamburg, Germany (English)	71 (32)	NR	9.35± 0.60	EG: Run + jump + resistance exercises (aerobic-based) CG: Usual care	45	3	10	② (Letter Digit Span)	No No
Purohit and Pradhan (2016)	Bengaluru, India (English)	72 (30)	NR	12.69 ± 1.35	EG: Yoga (motor skill-based) CG: Usual care	90	4	12	① (Stroop Test) ③ (More-odd shifting)	No No
Wang (2017)	Beijing, China (Chinese)	30 (14)	NR	5–6	EG: Tennis (motor skill-based) CG: Usual care	60	2	8	① (Flanker task) ② (1-back)	No No
Yin et al. (2018)	Beijing, China (Chinese)	326 (165)	NR	7–9	EG: Run (aerobic-based) EG: Taijiquan (aerobic-based) CG: Usual care	30	3–5	20	① (Flanker task) ② (1-back) ③ (More-odd shifting)	No No
Chaddock-Heyman et al. (2013)	Urbana, USA (English)	26 (11)	2.32 (1.09)	NR	EG: Bicycle (aerobic-based) CG: Usual care	76.8	5	22	② (1-back) ③ (More-odd shifting)	No No
Stroth et al. (2009)	Ulm, Germany (English)	35 (NR)	NR	14.20 ± 0.50	EG: Aerobic exercises CG: Usual care	40	3	12	② (1-back)	No No
Lina (2017)	Yangzhou, China (Chinese)	17 (9)	NR	11.37 ± 1.53	EG: Run (aerobic-based) CG: Usual care	30	4	11	② (0-back)	No No
Yan Jun and Chen (2013)	Yangzhou, China (Chinese)	87 (42)	NR	9.50 ± 0.30	EG: Aerobic dance CG: Usual care	30	3	12	① (Flanker task) ② (1-back) ③ (More-odd shifting)	No No
Keita et al. (2011)	Illinois, USA (English)	36 (19)	NR	7–9	EG: Medicine balls + resistance exercises (combining aerobic and muscular activity) CG: Usual care	70	5	24	② (Reaction time)	No No

(Continued)

TABLE 2 | Continued

Reference	Location (language)	Participant characteristics			Intervention program	Intervention characteristics			Outcome measured	Adverse event; follow-up
		N (male)	SES	Mean age or age range		Time (min)	Frequency (weekly)	Duration (week)		
Hillman et al. (2014)	Illinois, USA (English)	221 (NR)	NR	8–9	EG: Yoga + run (aerobic-based) CG: Usual care	70	5	24	① (Flanker task) ③ (Cognitive flexibility)	No No
Telles et al. (2013)	Uttarakhand, India (English)	98 (60)	NR	10.50 ± 1.30	EG: Yoga (aerobic-based) CG: Usual care	45	5	12	① (Stroop Test)	No Yes
Fisher et al. (2011)	Glasgow, UK (English)	64 (29)	7(1)	6.10± 0.30	EG: Run (aerobic-based) CG: Usual care	120		10	② (Reaction time)	No Yes
Tarp et al. (2016)	Rotterdam, Netherlands (English)	698 (309)	NR	12.90± 0.60	EG: Whole-body movement games CG: Usual care	60	4	12	② (Reaction time)	No Yes
Ludyga et al. (2017)	Basel, Switzerland (English)	36 (18)	NR	12-15	EG: Medicine balls + relay games (combining aerobic and coordinative exercises)	5-10	5	8	① (Stroop Test)	No Yes
Nie (2019)	Nanjing, China (Chinese)	40 (19)	NR	13.81± 0.30	EG: Wuqinxi (aerobic-based) CG: Usual care	45	3	8	① (Flanker task) ② (1-back) ③ (More-odd shifting)	No Yes
Egger et al. (2019)	Bern, Switzerland (English)	142 (70)	NR	7.91± 0.40	EG: Better ideas through exercises (aerobic-based) CG: Usual care	20	5	20	① (Flanker task)	No No
Vera et al. (2019)	Netherlands, Amsterdam (English)	201 (108)	NR	10.90± 0.70	EG: Dance (aerobic-based) CG: Usual care	10	5	9	① (Stroop Test)	No No

NR = not reported; EG = experimental group; CG = control group; SES = socioeconomic status; ① represents inhibitory control; ② represents working memory; ③ represents cognitive flexibility.

TABLE 3 | Physiotherapy Evidence Database Scale (PEDro) of the included randomized controlled trials (acute exercises and chronic exercises).

Author [Reference]	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Score
Benzing et al. (2016)	1	1	0	1	0	0	1	1	1	1	7
Pate (2015)	1	1	0	0	0	0	1	1	1	1	6
Gothe et al. (2013)	1	1	0	0	0	0	1	1	1	1	6
Chen et al. (2015)	1	1	0	1	0	0	1	1	1	1	7
Ellemberg and St-Louis-Deschênes (2010)	0	1	1	1	0	0	1	1	1	1	7
Jager et al. (2015)	1	1	0	0	1	1	1	1	1	1	8
Kubesch et al. (2009)	1	1	1	1	0	0	1	1	1	1	8
Chun et al. (2015)	1	1	0	1	1	0	1	1	1	1	8
Budde et al. (2010)	1	1	0	1	0	0	1	1	1	1	6
Yan et al. (2014)	0	1	0	1	0	1	1	1	1	1	7
Cooper et al. (2018)	1	1	0	1	0	0	1	1	1	1	7
Park and Etnier (2019)	1	1	0	1	0	0	1	1	1	1	7
Egger et al. (2018)	1	1	0	1	0	0	1	1	1	1	7
Vera et al. (2018)											
Vera et al. (2018)	1	1	0	1	0	0	1	1	1	1	7
Mean Score (acute exercises)											**7.00**
Chen et al. (2016)	1	1	0	1	1	1	1	1	1	1	9
De Greeff et al. (2016)	0	1	0	1	0	0	1	1	1	1	6
Kval et al. (2017)	1	1	0	1	0	0	1	1	1	1	7
Jiang (2015)	1	1	0	0	0	0	1	1	1	1	6
Xin (2012)	0	1	0	1	0	0	1	1	1	1	6
Budde et al. (2016)	1	1	1	1	0	0	1	1	1	1	8
Purohit and Pradhan (2016)	0	1	0	0	0	0	1	1	1	1	5
Wang (2017)	0	1	0	1	0	0	1	1	1	1	6
Yin et al. (2018)	1	1	0	1	1	0	1	1	1	1	8
Chaddock-Heyman et al. (2013)	1	1	0	1	0	0	1	1	1	1	7
Stroth et al. (2009)	1	1	0	0	0	0	1	1	1	0	5
Lina (2017)	0	1	0	1	0	0	1	1	1	1	6
Yan Jun and Chen (2013)	0	1	0	0	0	0	1	1	1	1	5
Keita et al. (2011)	0	1	0	1	0	0	1	1	1	1	6
Hillman et al. (2014)	1	1	1	1	1	0	1	1	1	1	9
Telles et al. (2013)	1	1	1	1	1	1	1	1	1	1	10
Fisher et al. (2011)	0	1	0	1	1	1	0	1	1	1	7
Tarp et al. (2016)	0	1	0	1	0	0	0	1	1	1	5
Ludyga et al. (2018)	1	1	0	1	0	0	1	1	1	1	7
Nie (2019)	1	1	0	1	0	0	1	1	1	1	7
Egger et al. (2019)	1	1	0	1	0	0	1	1	1	1	7
Vera et al. (2018)	1	1	0	1	0	0	1	1	1	1	7
Mean Score (chronic exercises)											**6.77**

Item 1 = eligibility criteria; Item 2 = randomization; Item 3 = concealed allocation; Item 4 = similar baseline; Item 5 = assessor blindness; Item 6 = subject blindness; Item 7 = a retention rate of 85% or above; Item 8 = comparison between groups; Item 9 = point measure and measures of variability; Item 10 = completeness of measurement results ("1" means that the corresponding item was explicitly described and present in details; "0" means that the corresponding item was absent, inadequately described, or unclear).

indicated less time being required for working memory. The aggregated result showed a significant benefit in favor of acute exercises on working memory (SMD = −0.72; 95% CI −0.89 to −0.56, $I^2 = 10.9\%$, $p < 0.001$) (**Figure 4**). Chronic exercises were shown to shorten the response time effectively (SMD = −0.54; 95% CI −0.74 to −0.33, $I^2 = 63.4\%$, $p < 0.001$) (**Figure 5**). The SMDs of acute and chronic exercises were considered as moderate ESs.

Thirteen studies (14 pairwise comparisons) examined the effect of exercises on cognitive flexibility (as measured by more-odd shifting and the Wisconsin card sorting test). A higher negative value of the mean change score for the reaction time indicated less time being required for cognitive flexibility. The aggregated result showed a significant benefit in favor of acute exercises on cognitive flexibility (SMD = −0.34; 95% CI −0.55 to −0.14, $I^2 = 0\%$, $p < 0.005$) (**Figure 6**). Similarly, chronic exercises also had a significant effect on cognitive flexibility (SMD = −0.34, 95 % CI −0.48 to −0.20, $I^2 = 49.3\%$, $p < 0.001$) (**Figure 7**). The SMDs of acute and chronic exercises were considered as small ESs.

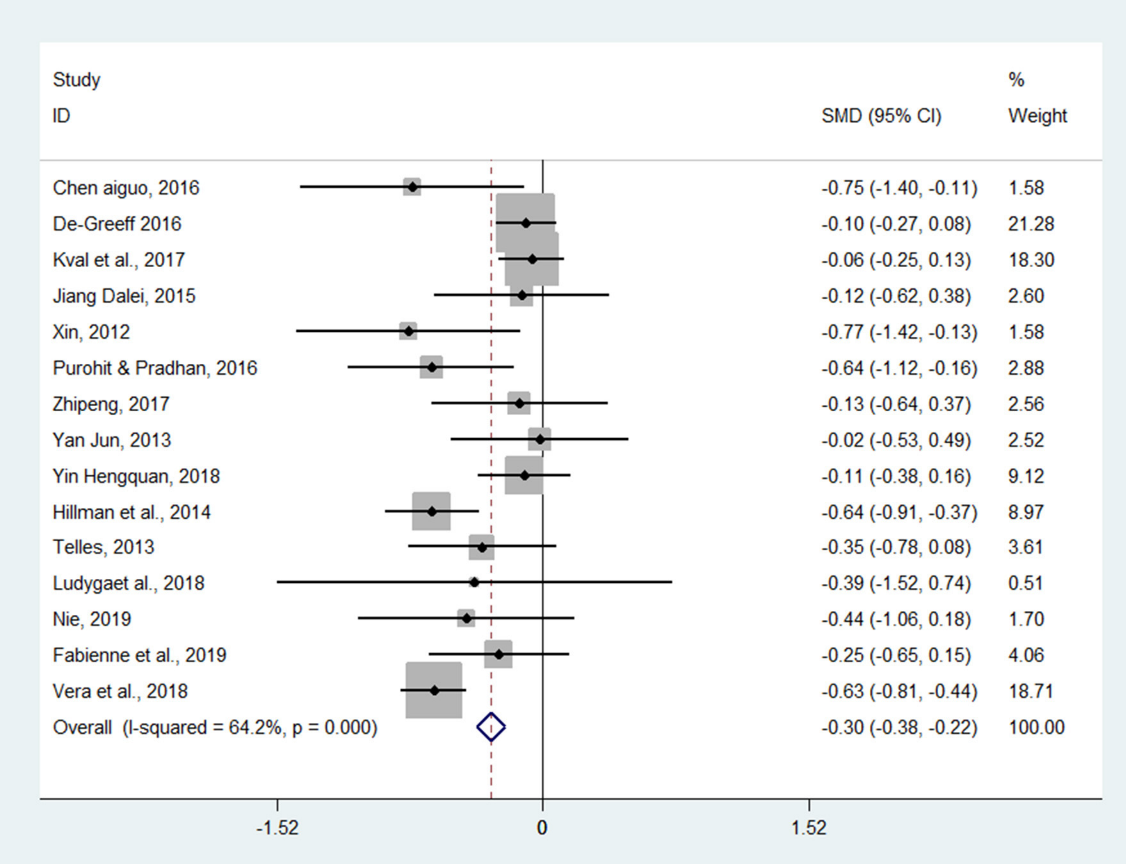

FIGURE 3 | The effect of chronic exercises on inhibitory control (SMD = standardized mean difference; CI = confidence interval).

GRADE Quality Evaluation

Based on the criteria of GRADE, the assessment of the certainty of the evidence regarding the significant impact of exercises on the subsets (inhibitory control, working memory, and cognitive flexibility) of executive functions in children and adolescents was separately evaluated (**Table 4**). Specifically, acute exercises exhibited medium-quality evidence for the working memory, inhibitory control, and cognitive flexibility of children and adolescents in their executive functions, whereas chronic exercises showed medium-quality evidence on inhibitory control and low-quality evidence on working memory and cognitive flexibility.

Moderator Analysis

For chronic exercises, variables (age, type, study quality, composite, frequency, time, and duration) are likely to be the influencing factors for children and adolescents on their inhibitory control and working memory. Moderator analysis using separate models was employed to examine potential sources of variance. All results are presented in **Table 3**.

Inhibitory Control Moderators

In terms of the composite type of intervention, either multiple exercise interventions or sole exercise interventions were employed in the original studies. There were no statistically significant differences on the ESs between the two types of interventions ($Q = 10.25$, $p = 0.001$) (**Table 5**). For chronic exercises, the sole exercise interventions had a significant improvement on inhibitory control (SMD =-0.55, 95% CI −0.83 to −0.25, $p < 0.001$) compared with the multiple exercise interventions (SMD = −0.16, 95% CI −0.27 to −0.06, $p < 0.001$). Furthermore, for intervention classification in the experimental group, open motor skills and closed motor skills were included in our current meta-analysis, showing a statistically significant difference in the ES ($Q = 14.49$, $p = 0.001$). The results showed a significant effect of open motor skills (SMD = −0.56, 95% CI −0.73 to −0.40) on inhibitory control. In terms of age, there was a statistically significant difference ($Q = 12.23$, $p = 0.01$). A large and significant reduction in the ES was attributed to children 12–18 years old (SMD = −0.81, 95% CI −1.15 to −0.48, $p < 0.001$) when compared with children 5–12 years old (SMD = −0.19, 95% CI −0.28 to −0.09, $p < 0.01$). Moreover, there were no significant differences in the duration ($Q = 0.07$, $p = 0.791$), frequency ($Q = 1.48$, $p = 0.224$), and exercise session time ($Q = 3.57$, $p = 0.110$). Similarly, the quality of studies did not produce a statistically significant difference between the two levels ($Q = 2.39$, $p = 0.124$).

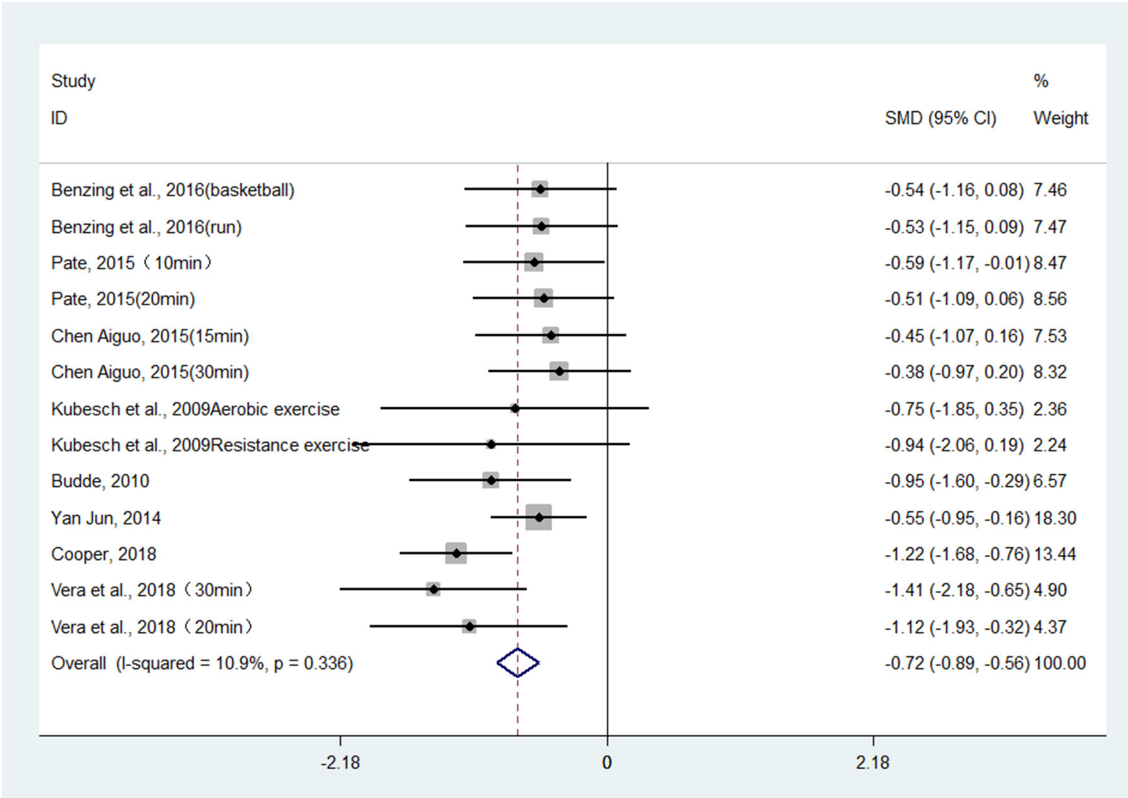

FIGURE 4 | The effect of acute exercises on working memory (SMD = standardized mean difference; CI = confidence interval).

Working Memory Moderators

In terms of intervention classification, a statistically significant difference of the evaluated ES was observed (Q = 20.53, $p = 0.001$) in open motor skills (SMD = −0.72, 95% CI −0.93 to −0.43, $p < 0.001$) and closed motor skills (SMD = −0.31, 95% CI −0.57 to −0.25, $p < 0.01$) (**Table 6**). In terms of the composite type of intervention, the two types of composite (multiple exercise interventions and sole exercise interventions) did not contribute to statistically significant differences for the ES estimate (Q = 1.47, $p = 0.257$), where both multiple exercise interventions (SMD =-0.58, 95% CI −1.15 to −0.37, $p < 0.001$) and sole exercise interventions (SMD = −0.44, 95% CI −0.83 to −0.25, $p < 0.001$) led to significant improvements in working memory. Notably, study quality produced a significant difference in working memory (Q = 27.89, $p = 0.001$). A study quality score of more than 6 had a small and significant ES (SMD = −0.33, 95% CI −0.55 to −0.21, $p < 0.01$). By contrast, a large and significant ES on working memory was found in favor of studies with a quality score of <6 (SMD = −0.86, 95% CI −1.13 to −0.39, $p < 0.01$). In addition, the factor of age contributed to statistically significant differences for the ES estimate (Q = 18.06, $p = 0.001$); children 5–12 years old had a greater improvement in working memory (SMD = −0.64, 95% CI −0.87 to −0.42, $p < 0.001$) than those 12–18 years old (SMD = −0.30, 95% CI −0.49 to −0.12, $p < 0.001$). Additionally, in terms of duration, frequency, and exercise session time, there was a statistically significant difference for exercise session time (Q = 18.92, $p = 0.001$). A moderate and significant reduction in the ES was attributed to the exercise session time (≤30 min, SMD =-0.82, 95% CI −1.01 to −0.64, $p < 0.001$) when compared with prolonged exercise (>30 min), which contributed to a small ES (SMD =0.35, 95% CI −0.47 to −0.22, $p < 0.001$). By contrast, statistically significant differences of the evaluated ESs were not observed for duration (Q = 0.16, $p = 0.694$) and frequency (Q = 0.10, $p = 0.953$).

Meta-Regression Analysis

In order to examine the effect of chronic exercises on inhibitory control and working memory, meta-regression analyses were performed to determine if the variables (age, type, study quality, composite, frequency, time, and duration) influenced the different indices in **Tables 7**, **8**. Regression results showed that open motor skill interventions ($\beta = 0.451645$, Q = 1.82, df = 1, $p = 0.007$) and age ($\beta = -0.608123$, Q = 2.51, df = 1, $p = 0.029$) were significantly associated with inhibitory control. However, we found no significant relationship between composite interventions and dependent variables on inhibitory control ($\beta = 0.406159$, Q = 2.06, df = 1, $p = 0.064$).

Regarding the effects of chronic exercises on working memory, both type ($\beta = -0.375588$, Q = 3.57, df = 1, $p = 0.024$) and study quality (β =-0.555877, Q = 5.28, df = 1, $p = 0.001$) influenced the ES. Notably, we found that age could significantly moderate the ES of working memory ($\beta = 0.293404$, Q = 4.57,

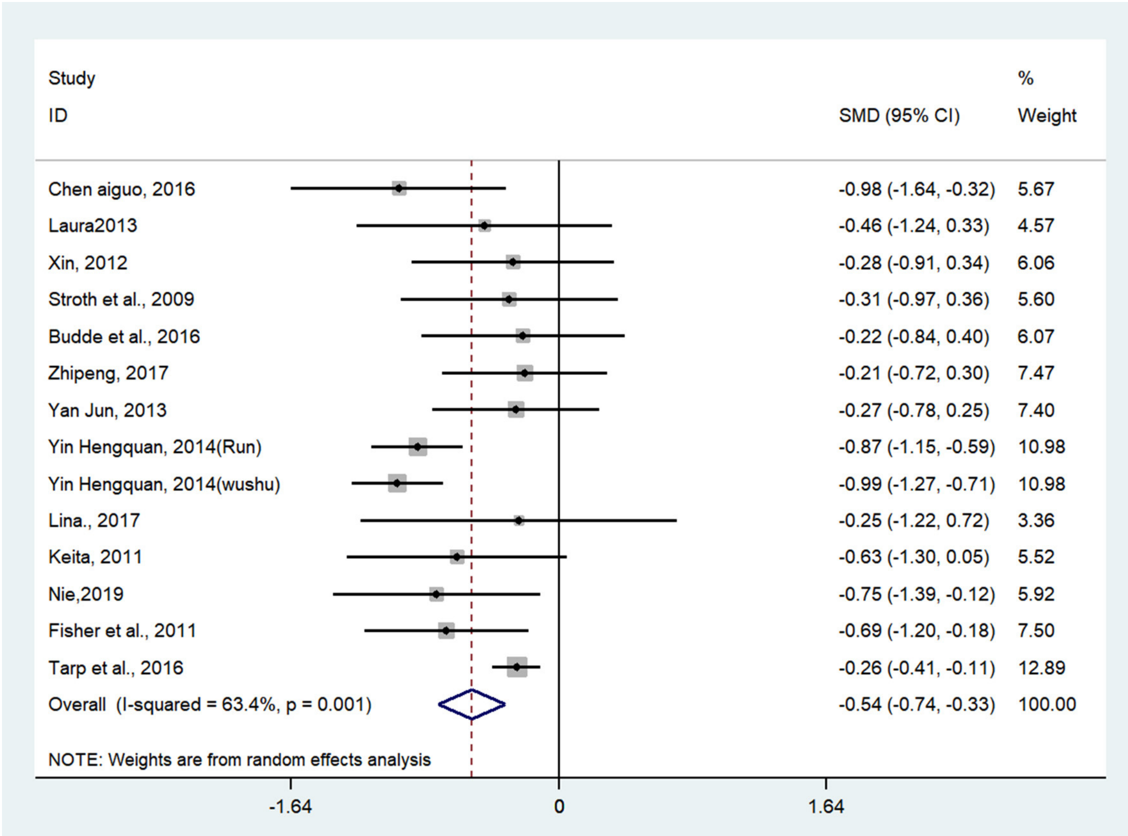

FIGURE 5 | The effect of chronic exercises on working memory (SMD = standardized mean difference; CI = confidence interval).

df = 1, p = 0.033). Additionally, there was no significant relationship between exercise session time and chronic exercises on working memory ($\beta = 0.303556$, Q = 1.71, df = 1, $p = 0.115$).

DISCUSSION

Summary of Evidence

The present meta-analysis suggests that both acute and chronic exercises may be effective for improving executive functions (e.g., inhibitory control, working memory, and cognitive flexibility) in healthy child and adolescent populations. Moreover, in chronic exercise interventions, working memory was moderated by age, exercise type, and study quality, while only two variables (age and exercise type) played a moderating role in inhibitory control.

Inhibitory Control

Inhibitory control refers to the conscious inhibition or automatic response in the cognitive process (Wright et al., 2010). The Stroop, Go/no-go, and Flanker tasks are the most commonly used tools to evaluate the performance (reaction time and/or accuracy) of inhibitory control (Chen et al., 2020). The present review suggests that both acute and chronic exercises are beneficial for inhibitory control, with small magnitudes (Xue et al., 2019; Li et al., 2020). The mechanisms of action of acute and chronic exercises on inhibitory control are unclear, but a possible explanation regarding the effects is attributed to the features of exercises; that is, whether acute or chronic exercises are used can cause an individual to need to complete more complex tasks than everyday multitasking, and this operation mode relies on the non-automatic selection of the process during exercises, which facilitates the speed of reaction of inhibition control (Li et al., 2017). Furthermore, a prior study suggested that acute exercises could significantly improve the speed of reaction of inhibitory control in children and adolescents (Ludyga et al., 2016), and a recent study suggested that chronic exercises are equal to the cumulative effect of acute exercises, while the increase in cognitive performance after chronic exercise interventions seems to be reasonable (Pesce, 2012). Therefore, further studies will be needed to identify the relationship between the influence mechanisms of acute exercises and chronic exercises on inhibitory control.

It is common that heterogeneity across studies is present in the meta-analysis, but the impact of acute exercises on the inhibitory control has a small heterogeneity, which is not in agreement with other acute exercise intervention review studies (Moreau and Chou, 2019). This may be due to the fact that our inclusion criteria only included healthy children and adolescents, and evaluation in acute exercise research is

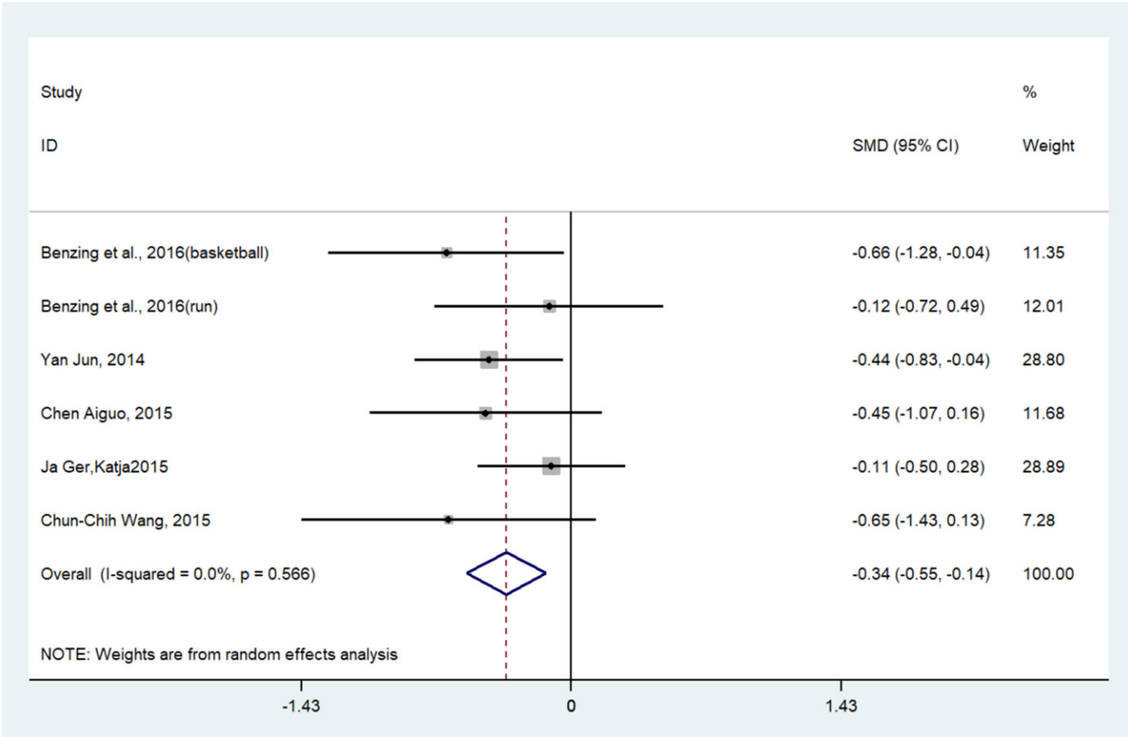

FIGURE 6 | The effect of acute exercises on cognitive flexibility (SMD = standardized mean difference; CI = confidence interval).

carried out immediately after the intervention, which leads to less heterogeneity between different studies. On the contrary, there was considerable heterogeneity regarding the effect of chronic exercises on inhibitory control ($I^2 = 68.20\%$). Meta-regression showed that age and intervention types were moderators of the effect of chronic exercises on inhibitory control, implying that the effect of chronic exercises on inhibitory control improved with age.

Furthermore, the subgroup analysis indicated that, from the age perspective, although 5–12-year-old children and 12–18-year-old adolescents showed positive effects in terms of improving inhibitory control, 5–12-year-old children showed a low inhibitory ability compared with 12–18-year-old adolescents. This finding is in agreement with a previous study (Harnishfeger, 1995) that showed that there is an obvious age trend in the development of inhibition: children between 5 and 10 years of age had a very low inhibition ability, children over 10 years of age began to approach adults, and adults had the strongest inhibition ability (Harnishfeger, 1995). In addition, from the study intervention characteristic perspective, open motor skills can improve inhibition ability significantly more than closed motor skills ($p = 0.001$). This is attributed to the fact that open skills need to respond consistently to changing circumstances. In the process of implementation, information processing methods such as perception, pattern recognition, and decision-making are more prominent than in closed skill exercises, and the level of self-regulation is higher, resulting in significant inhibitory control. A recent meta-analysis demonstrated that the strongest effects emerged from aerobic exercises (motor skills) and cognitively engaging exercises (yoga combined with meditation and stretching) (Vazou et al., 2019). Moreover, a prior study suggested that cognitively engaging physical activity and mentally enriching interventions may promote fundamental changes in the brain that benefit cognition in children (Hillman et al., 2014). These findings indicated that more advanced strategies and cognitive motor skills can contribute to improving inhibitory control for normal child and adolescent populations. Finally, our results showed that medium effect sizes emerged from chronic exercise programs focused on sole exercise interventions (i.e., football, tennis, yoga, wuqinxi). It is important to emphasize that the interpretation of the results from comparisons between sole exercises and multiple exercises of physical activity programs should be conducted with caution due to the small number of studies included in this review.

In addition, the experimental intervention characteristics involving duration, frequency, and exercise session time were not moderators of the effect of chronic exercises on inhibitory control ($p > 0.05$). However, as we found those studies had no long-term follow-up, it remains unclear whether a potential benefit will emerge after a longer period after intervention with chronic exercises on inhibitory control. Therefore, we should not make any definitive claims with respect to composite types and experimental intervention characteristics for chronic exercises in this systematic review.

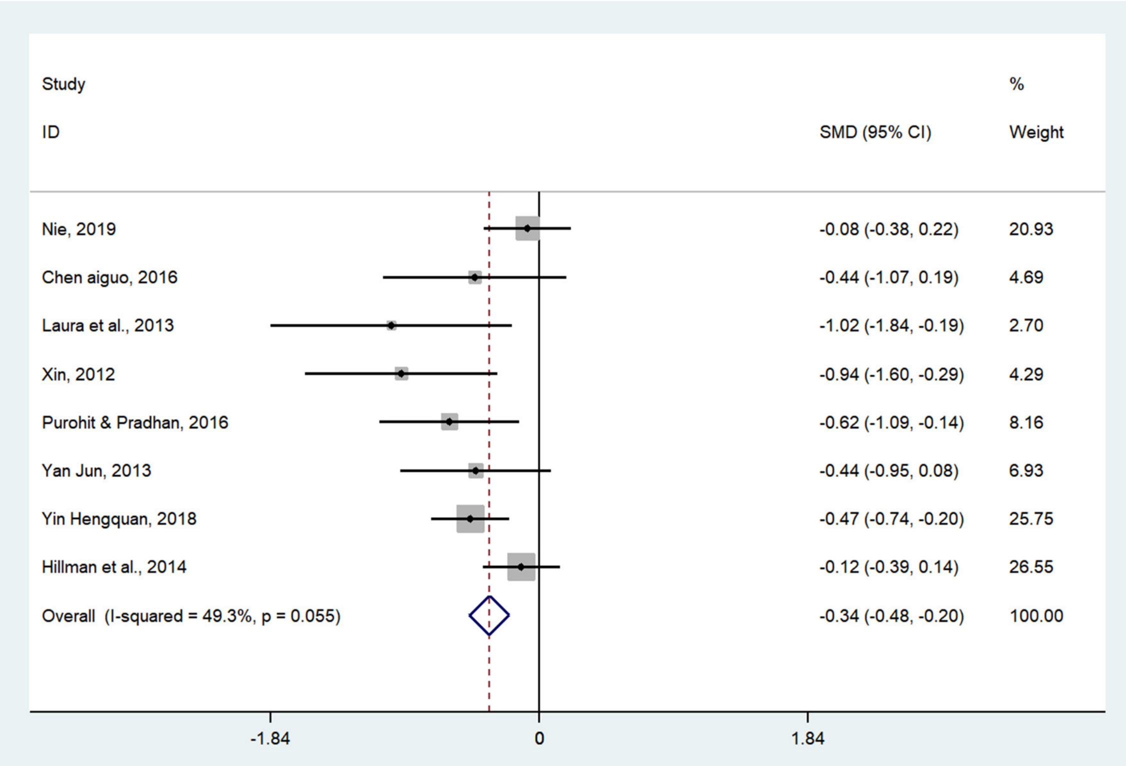

FIGURE 7 | The effect of chronic exercises on cognitive flexibility (SMD = standardized mean difference; CI = confidence interval).

Working Memory

Working memory mainly measures the preservation and update of information, and the digit span forward, digit span backward, letter digit span, Tower of London, and N-back task (1-back and 2-back) measurement tools are the most commonly used to evaluate the response time of working memory (Chen et al., 2020). The aggregated results of the present meta-analysis show that acute and chronic exercises are beneficial for working memory in children and adolescents (the magnitude of the effects were statistically significant), and the calculated ESs were −0.72 (acute exercises) and −0.54 (chronic exercises), which have similar medium efficacies for improving working memory. A prior study suggested that acute aerobic exercises have an intensity dose effect on memory in children and adolescents (Rathore and Lom, 2017). Furthermore, early meta regression analysis studies also found that acute aerobic exercises have a promoting effect on memory, and the effect size is greater than that of acute exercises affecting inhibitory control and information processing speed (Lambourne and Tomporowski, 2010). In addition, according to the international physical activity guidelines, chronic exercises are very cognitively beneficial (Schmidt et al., 2015), and a prior study suggested that the cardiorespiratory fitness level of chronic exercises is helpful for the 1-back reaction speed (Luo, 2018). However, regarding the differences between the intervention effects of chronic exercises and acute exercises, the results of a previous study (Rathore and Lom, 2017) are inconsistent with our research results due to the inclusion of older adults, while our criteria include only children and adolescents. Furthermore, some previous studies have suggested that acute exercises have no effect on working memory (Li et al., 2017; De Greeff et al., 2018). Similarly, a prior study suggested that working memory showed no improvement across a range of intervention durations (5–20 min) and intensities (Daly-Smith et al., 2018). The reason for the difference in these results is due to our working memory measurement index extraction method, which only revolved around the processing speed without considering accuracy. The current meta-analysis shows that moderate to high intensity and time (20–30 min) physical activity is effective at enhancing the response time of working memory. Although the mechanisms of action of acute and chronic exercises on working memory are unclear, the contrasting results between chronic and acute exercises offer interesting future directions to explore different mechanisms that govern both intervention types, and need further study.

In addition, our results show that acute exercises were characterized by non-significant heterogeneity ($I^2 = 24.4\%$), which indicates that the 11 studies were not significantly dissimilar from each other, adding further confidence to the result. By contrast, the meta-analysis of the 14 chronic exercise studies revealed a significant heterogeneity ($I^2 = 63.4\%$). Meta-regression showed that study quality and intervention type were

TABLE 4 | Grading Recommendations to Assess Development and Evaluation (GRADE) assessment of the evidence of certainty for exercise effects.

Outcomes		Presence of downgrading item of GRADE					Level of certainty of evidence
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	
Chronic exercises	Inhibitory control	Yes	No	No	No	No	II (moderate) (1)
	Working memory	Yes	No	No	Yes	No	III (low) (1) (4)
	Cognitive flexibility	Yes	No	No	Yes	No	III (low) (1) (4)
Acute exercises	Inhibitory control	Yes	No	No	No	No	II (moderate) (1)
	Working memory	Yes	No	No	No	No	II (moderate) (1)
	Cognitive flexibility	Yes	No	No	No	No	II (moderate) (1)

(1) Risk of bias: if the risk of bias of the included studies is present in the meta-analysis, e.g., randomization, concealed allocation, or blinding of assessors/subjects; (2) Inconsistency: point estimates are concentrated, confidence intervals can overlap, and the results of the heterogeneity tests are not statistically significant; (3) Indirectness: present if the intervention studied in the meta-analysis is not directly relevant to the outcome; (4) Imprecision: present if the sum of sample sizes of all individual studies included in the meta-analysis is less than 500, and if the effect size's 95% CI is comparatively large; (5) Publication bias: present if the author only searched the Chinese database, or only one database.

TABLE 5 | Subgroup analysis of inhibitory control (chronic exercises). SMD: standardized mean difference.

Subgroup	*N*	SMD	95% conf. interval	I^2	Test for between-group heterogeneity		
					Q-value	df (Q)	*p*-value
Age							
5–12	11 (1567)	−0.20	−0.28, −0.09	50.8%	12.23	1	0.001
12–18	3 (148)	−0.81	−1.15, −0.48	72.5%			
Type							
Open motor skills	9 (859)	−0.56	−0.73, −0.40	60.1%	14.49	1	0.001
Closed motor skills	6 (856)	−0.11	−0.22, 0.00	0.0%			
Study quality							
Scores more than 6 (>6)	8 (716)	−0.32	−0.55, −0.20	25.2%	2.39	1	0.124
Scores less than 6 (≤6)	7(998)	−0.18	−0.31, −0.06	84.7%			
Duration							
More than 12 weeks	7 (545)	−0.22	−0.36, −0.09	69.6%	0.07	1	0.791
Less than 12 weeks	8(1170)	−0.25	−0.37, −0.12	72.8%			
Composite type							
Multiple exercises intervention	7 (713)	−0.16	−0.27, −0.06	64.2%	10.25	1	0.001
Sole exercises intervention	8 (1002)	−0.55	−0.83, −0.25	55.8%			
Frequency							
1–3 times/week	5(442)	−0.14	−0.25, −0.05	69.0%	1.48	1	0.224
4–7 times/week	10(1273)	−0.42	−0.58,−0.27	49.8%			
Exercise session time							
≤30	5(489)	−0.12	−0.24, 0.05	0.0%	3.57	1	0.110
>30	10(1226)	−0.47	−0.73, −0.21	70.0%			

moderators of the effect of chronic exercises on working memory. Moderator analysis suggested that a significant difference in working memory between a study quality with a score more than six and a study quality with a score <6 was observed, which implies that a less rigorous study design may consciously affect the results, thus exaggerating the effect of the intervention and resulting in a large effect size. In addition, similarly to the inhibitory control influence mechanism, open motor skills exercises may also significantly improve the reaction of working memory.

Furthermore, experimental intervention characteristics involving duration, frequency, and exercise session time are crucial to investigating the effects of chronic exercise changes in working memory. The moderator analysis indicated that each session time of ≤30 min can improve the response of large ES (−0.82) on working memory; the effect is more significant than for a session time of >30 min. A prior study suggested that the effect of aerobic exercises for 55 min is not as good as for 30 min (Fu and Fan, 2016). The possible reason for this is that an excessively long exercise time cannot induce an appropriate level of arousal and results in fatigue (Moreau and Chou, 2019). Additionally, duration (<12 weeks) and frequency (one to three times) could significantly contribute to moderate ESs on working memory; chronic exercises more than four times per week and

TABLE 6 | Subgroup analysis of working memory (chronic exercises).

Subgroup	*N*	SMD	95% conf. interval	I^2	Test for between-group heterogeneity		
					Q-value	df (Q)	*p*-value
Age							
5–12	9 (638)	−0.64	−0.87, −0.42	47.0%	18.06	1	0.001
12–18	3 (773)	−0.30	−0.49, −0.12	12.8%			
Type							
Open motor skills	5 (419)	−0.72	−0.93, −0.43	26.9%	20.53	1	0.001
Close motor skills	5 (386)	−0.31	−0.57,−0.25	12.4%			
Studies' quality							
Scores more than 6 (>6)	6 (884)	−0.33	−0.55, −0.21	6.9%	27.89	1	0.001
Scores less than 6 (≤6)	7 (593)	−0.86	−1.13, −0.39	0.0%			
Duration							
More than 12 weeks	6 (336)	−0.36	−0.79, −0.15	0.0%	0.16	1	0.694
Less than 12 weeks	7 (1141)	−0.62	−0.97,−0.26	82.8%			
Composite type							
Multiple-exercise intervention	6 (666)	−0.58	−1.15, −0.37	48.0%	1.47	1	0.257
Sole-exercise intervention	7 (811)	−0.44	−0.83, −0.25	23.2%			
Frequency							
1–3 times/week	5 (478)	−0.40	−0.65, −0.15	21.6%	0.10	1	0.953
4–7 times/week	8 (999)	−0.61	−0.61,−0.32	79.6%			
Exercise session time							
≤30	4 (295)	−0.82	−1.01, −0.64	59.5%	18.92	1	0.001
>30	9 (1182)	−0.35	−0.47, −0.22	13.1%			

TABLE 7 | Regression analysis for chronic exercises versus the control group of inhibitory control.

ES	No. of studies/ comparisons	Coef. (β)	Std. err.	95% conf. interval	Test for between-groupheterogeneity		
					Q-value	df (Q)	*p*-value
Age*	14	−0.608123	0.241830	−1.140387, −0.075859	2.51	1	0.029
Type**	15	0.451645	0.137132	0.149819, 0.753470	1.82	1	0.007
Study quality	15	−0.296366	0.229172	−0.800770, 0.208038	0.65	1	0.222
Duration	15	0.006166	0.243023	−0.528724, 0.541055	1.31	1	0.980
Frequency	15	−0.208072	0.225305	−0.703965, 0.287821	0.92	1	0.376
Time	15	−0.378365	0.222389	−1.330843, 0.923009	1.70	1	0.117
Composite	15	0.406159	0.197258	−0.028003, 0.840320	2.06	1	0.064

**shows that the data differ. *p < 0.05, **p < 0.01.*

TABLE 8 | Regression analysis for chronic exercises vs. the control group of working memory.

ES	No. of studies/ comparisons	Coef. (β)	Std. err.	95% conf. interval	Test for between-group heterogeneity		
					Q-value	df (Q)	*p*-value
Age	12	0.293404	0.263048	−0.225295, 0.683069	4.57	1	0.033
Type*	10	−0.375588	0.145919	−0.693518, −0.057659	3.57	1	0.024
Study quality**	13	−0.555877	0.105251	−0.785000, −0.326554	5.28	1	0.001
Duration	13	−0.036083	0.333311	−1.29879, −0.090172	0.11	1	0.921
Frequency	13	−0.113366	0.225896	−0.616694, 0.389962	0.50	1	0.627
Time	13	0.303556	0.177347	−0.086782, 0.693894	1.71	1	0.115
Composite	13	−0.235401	0.175217	−0.617166, 0.146365	1.34	1	0.204

**shows that the data differ. *p < 0.05, **p < 0.01.*

for more than 12 weeks did not significantly benefit working memory ($p_1 = 0.694$, $p_2 = 0.953$). The reason for this finding is not fully understood, because of the limited experimental design with no long-term follow-up. Therefore, we also should not make any definitive claim with respect to duration and frequency for chronic exercises in working memory. It is worth noting that from the age perspective, our current meta-analysis showed that the intervention effect for children aged 5–12 is greater than that for adolescents aged 12–18 ($p = 0.001$); this is the opposite of the result for the inhibitory control. This may be attributed to the fact that working memory extraction, attention distribution and focus of attention increase significantly at 6–9 years old (Wang et al., 2013), and children aged 5–12 can actively complete tasks in accordance with the teacher's requirements, which is also one of the reasons for their strong subjective initiative.

Cognitive Flexibility

Cognitive flexibility refers to the ability of individuals to constantly adjust their thoughts and behaviors in order to adapt to changing situations (Hernández et al., 2010). Specifically, when two tasks compete for the same cognitive resource, flexibility is the process of controlling the mutual conversion of these two tasks. The commonly used measurement tasks are as follows: the plus–minus task, number–letter task, more-odd shifting, the local–global task, and the Wisconsin card sorting test (WCST).

Because cognitive flexibility was present across a small number of eligible studies, the present meta-analysis only synthesized WCST and more-odd shifting. With respect to cognitive flexibility, a significant improvement in cognitive flexibility in the present meta-analysis was identified in favor of acute and chronic exercises, but the ES effects of the two types of exercises regarding cognitive flexibility were small (−0.34). It is reasonable that a significant improvement was observed for cognitive flexibility. That is because exercises intervention can change the brain's activation pattern, which specifically manifests as an increased activation of the bilateral upper frontal gyrus, bilateral middle frontal gyrus, and bilateral upper lobules, and an individual is prone to having activated pre-frontal and parietal lobes when exercising cognitive flexibility (Jamadar et al., 2010; Boucard et al., 2012). Therefore, appropriate exercises can improve cognitive flexibility. Although the positive effects of acute and chronic exercises on cognitive flexibility have been shown in the present meta-analysis, it is necessary to explore the literature evidence because of the small number of studies included.

Study Limitations

This study has a certain number of limitations and deficiencies. (1) There was a limited number of works on cognitive flexibility. Therefore, we could not obtain an accurate result regarding the effect of executive function interventions on children and adolescents. (2) The high-level executive functions, such as decision-making and reasoning, can be understood with a detailed assessment of the dynamics of EF performance, but the studies reviewed in this meta-analysis did not include this information. We believe that future studies should collect, retain, and ideally share these types of data to allow more detailed analyses. (3) Only three articles in this study explained random sequence generation in detail, and no other work mentioned the method of random allocation and hiding. (4) The intervention method in some of the included studies was aerobic exercises, which has not been explained in great detail, and thus we were unable to confirm which skills were involved in aerobic exercises. (5) Most studies had no long-term follow-up, and it remains unclear whether a potential benefit will emerge after a longer period post-intervention of chronic exercises in executive function. (6) The current meta-analysis only made relevant reports on the reaction time; in the future, we also need to report on the effect of physical activity on the accuracy of executive functions.

CONCLUSIONS

The results of the current meta-analysis demonstrate that acute and chronic exercises may have a positive effect on executive function for children and adolescents, especially in terms of working memory. To better understand the effects of acute and chronic exercises on children and adolescents, rigorous study designs are necessary. In addition, the impact of exercise training on cognitive flexibility needs to be further explored. We should explore the impact of long-term physical exercises on cognitive flexibility, which would also provide a reference for improving executive functions through exercises in the future.

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.

AUTHOR CONTRIBUTIONS

SL, ZL, and YC: conceptualization. SL and ZL: methodology, software, and resources. PC, QY, and YZ: validation. ZK, WL, YZ, and SC: formal analysis. SL, QY, and ZL: investigation and data curation. SL, ZL, and YC: writing—original draft preparation. QY, PC, YZ, ZK, WL, SC, and YC: writing—review and editing. All authors contributed to the article and approved the submitted version.

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Dual-Task Interference in a Simulated Driving Environment: Serial or Parallel Processing?

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When humans are required to perform two or more tasks concurrently, their performance declines as the tasks get closer together in time. Here, we investigated the mechanisms of this cognitive performance decline using a dual-task paradigm in a simulated driving environment, and using drift-diffusion modeling, examined if the two tasks are processed in a serial or a parallel manner. Participants performed a lane change task, along with an image discrimination task. We systematically varied the time difference between the onset of the two tasks (Stimulus Onset Asynchrony, SOA) and measured its effect on the amount of dual-task interference. Results showed that the reaction times (RTs) of the two tasks in the dual-task condition were higher than those in the single-task condition. SOA influenced the RTs of both tasks when they were presented second and the RTs of the image discrimination task when it was presented first. Results of drift-diffusion modeling indicated that dual-task performance affects both the rate of evidence accumulation and the delays outside the evidence accumulation period. These results suggest that a hybrid model containing features of both parallel and serial processing best accounts for the results. Next, manipulating the predictability of the order of the two tasks, we showed that in unpredictable conditions, the order of the response to the two tasks changes, causing attenuation in the effect of SOA. Together, our findings suggest higher-level executive functions are involved in managing the resources and controlling the processing of the tasks during dual-task performance in naturalistic settings.

Keywords: dual-task interference, driving, drift diffusion model, task order predictability, dual-task theories

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INTRODUCTION

Humans have limited cognitive capacity. They can only attend to a few items in the scene (Pylyshyn and Storm, 1988; Huang et al., 2007), maintain and manipulate a few items in working memory (Kane and Engle, 2000; Engle, 2002), have limits in the amount of information they can store in short and long term memory (Anderson et al., 1996), and their performance is hindered when they are asked to handle multiple demands in close temporal proximity (Pashler, 1994a). One of the manifestations of this limited capacity is dual-task interference. When performing two tasks concurrently, reaction times increase and accuracies decrease as the two tasks get close together in time (Pashler and Johnston, 1989). During driving, this phenomenon manifests itself in performance declines when drivers attempt to drive and perform a secondary task simultaneously (Horrey and Wickens, 2004; Blanco et al., 2006; Strayer et al., 2017). Despite the importance of dual-task interference in everyday tasks such as driving and its potentially fatal consequences (Bakhit et al., 2018), most studies of dual-task interference have used artificial paradigms to investigate the underlying mechanisms of dual-task interference (Sigman and Dehaene, 2005, 2008; Miller et al., 2009). In this study, taking the artificial designs one step closer to the natural task of driving, we aim to examine the underlying mechanisms of dual-task interference in a simulated driving environment.

To systematically investigate dual-task interference in artificial tasks (Pashler and Johnston, 1989; Pashler, 1994a), the time interval between the onsets of the first and the second stimulus (henceforth referred to as the Stimulus Onset Asynchrony or SOA) has been varied. It has been shown that when the SOA decreases, the RTs increase and the accuracies decrease. This performance decline as a function of SOA has been used as a measure of dual-task interference. A couple of studies using a simulated driving environment have shown similar effects of SOA on dual-task interference (Levy et al., 2006; Hibberd et al., 2013). These studies provide evidence for dual-task interference in driving, but they do not shed light on its underlying mechanisms.

Several theories have been proposed to explain the dual-task interference; the two most influential of them are the "bottleneck theory" and the "central capacity sharing theory." According to the bottleneck theory, dual-task interference appears when the two tasks rely on the same processor. In this theory, this processor at any time can only be occupied by one of the two tasks (Pashler, 1994a). When the first task is being processed, the second task must wait for the first one to be finished so that the processor is released. Dividing each task into three stages of (1) perceptual, (2) response selection or decision, and (3) motor execution, the bottleneck theory proposes that the stimulus perception and the motor execution stages could be performed in parallel, while the decision stage is the bottleneck that could only process the two tasks in a serial manner (McCann and Johnston, 1992; Sigman and Dehaene, 2008). Many studies have proposed evidence in favor of the bottleneck theory (Pashler and Johnston, 1989; Pashler, 1994b; Ruthruff et al., 2001; Sigman and Dehaene, 2005). This theory predicts that the dual-task interference only affects the RT of the second task and has no effect on the response of the first task because the first task is processed by the decision stage first and postpones the processing of the second task (Pashler, 1994a).

On the other hand, the central capacity-sharing theory suggests that the limitation in the processing capacity is the main reason for dual-task interference. Unlike the bottleneck theory that assumes serial processing of the two tasks, this theory suggests that in the dual-task conditions, all three stages of perceptual, decision, and motor execution could process the two tasks in parallel (Posner and Boies, 1971; Kahneman, 1973; McLeod, 1977; Duncan, 1980). In this theory, only the decision process is limited in capacity, while there are no resource limitations for the perceptual and motor execution stages (Tombu and Jolicoeur, 2003). This theory predicts that dual-task interference affects the RT of both the first and the second tasks and that the size of this reaction time change depends on the size of the sharing portion. Several studies have provided evidence in favor of the capacity sharing theory. Some have observed a robust effect of dual-task interference on the RT of both the first and the second tasks (Carrier and Pashler, 1995; Tombu and Jolicoeur, 2002; Oriet et al., 2005; Sigman and Dehaene, 2006; Zylberberg et al., 2012).

Recently, Zylberberg et al. (2012) proposed a hybrid model for dual-task processing. They suggested that the decision stage of the two tasks is processed in parallel, while there exists a bottleneck in mapping the decision to the motor responses (**Figure 1D**). Zylberberg et al. (2012) used drift diffusion model (DDM) in a dual-task paradigm and showed that the drift rate and the post-decision time increase for the second task during dual-task interference. To do this, they used two simple artificial tasks. Currently, it is not clear whether these findings in artificial tasks could be generalized to real-world tasks such as driving. In the current study, we aimed to extend these findings to a naturalistic setting and investigate the nature of dual-task interference in our simulated driving environment. To do this, we explored the effect of SOA on driving performance and used a DDM to investigate if the driving and the secondary task are performed serially (as proposed by the central bottleneck theory) or in parallel (as proposed by the capacity sharing theory) or if a hybrid model best accounts for the results (as proposed by the Zylberberg et al., 2012).

A DDM could be used as a framework to model the different processing stages of two-choice tasks (Ratcliff, 1978, 2015; Ratcliff and Rouder, 1998). This model assumes that during a two-choice decision task, evidence accumulates gradually to reach one of two decision thresholds corresponding to the two choices. The perceptual, motor, and other non-decision related stages of task processing are modeled as the non-decision time in the DDM (henceforth referred to as non-decision time; **Figure 1**). The predictions of the bottleneck and the capacity sharing theories can be restated within the framework of the DDM. The bottleneck theory assumes that the decision stage of the two tasks is processed separately and sequentially and that at shorter SOAs, the processing of the decision stage of the second task is delayed until the decision stage of the first task is completed (**Figure 1B**). In other words, this theory predicts that the rate of evidence accumulation (drift rate) for the two tasks is constant across SOAs, while there is a delay before the start of evidence accumulation for the second task that translates to increased non-decision time at shorter SOAs. On the other hand, the capacity sharing theory suggests that the decision process for the two tasks are performed concurrently, and the resources for decision making are shared between the two tasks (**Figure 1C**). Therefore, this theory predicts a decrease in the rate of evidence accumulation of the two tasks at shorter SOAs and a constant non-decision time across SOAs. A hybrid account will have signatures of both bottleneck and capacity sharing theories, showing a decrease in the rate of evidence accumulation as well as an increased non-decision time.

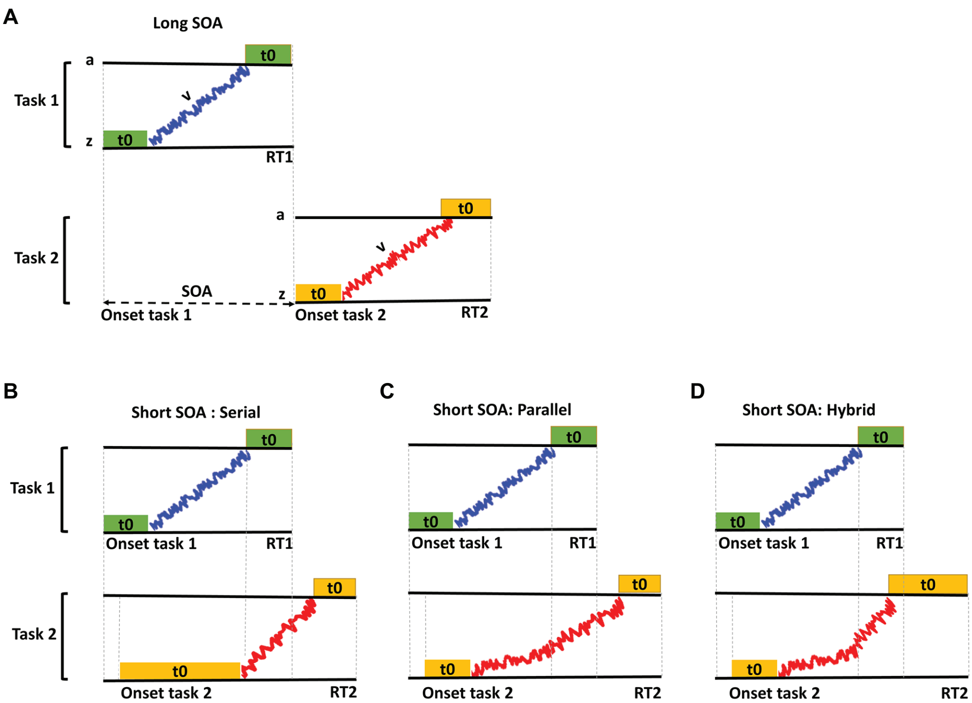

FIGURE 1 | A schematic of drift-diffusion modeling based on the predictions of the bottleneck, capacity sharing theories and a recent hybrid model proposed by Zylbelberg et al. (2012). *V* denotes the noisy evidence accumulation process (drift rate) in the decision stage of the two tasks, *t0* denotes the non-decision time and *a* and *z* denote the decision threshold and the initial state of the decision processes, respectively. Here, only one threshold is shown, but there are two decision thresholds in the drift-diffusion model corresponding to the two alternatives of the two-choice tasks. **(A)** The processing stages of Task 1 (top) and Task 2 (bottom) in the long SOA condition. In the long SOA, the two tasks are processed independently, and there is no interference between the two tasks. **(B)** The processing stages of task 1 and task 2 in the short SOA based on the predictions of the bottleneck theory that suggests the evidence accumulation for Task 2 does not begin until that for Task 1 is complete. **(C)** The processing stages of Task 1 and Task 2 in the short SOA condition based on the predictions of the capacity sharing theory that suggests that the evidence accumulation for the two tasks happens simultaneously and in parallel but at slower rates compared to the long SOA conditions. **(D)** The processing stages of Task 1 and Task 2 in the short SOA condition based on the predictions of the hybrid model that suggests that the evidence accumulation for the two tasks happens simultaneously and in parallel but at slower rates and, in addition, a delay exists in the mapping of the decision to motor response in the short compared to the long SOA conditions.

Evidence for or against dual-task theories is mostly gathered through simple tasks. Typical examples include visual discrimination tasks (e.g., object, color, and orientation discrimination) or tone discrimination tasks (e.g., high pitch vs. low pitch). The predictions of these theories have not been sufficiently tested in more naturalistic, real-world conditions. Several differences exist between artificial tasks and real-world tasks such as driving. Examples of these include: (1) in the real-world driving situations, people often need to perform two or more motor movements sequentially to complete each driving task. For example, when the driver decides to turn right/left, he/she should rotate the wheel to turn the car to the correct location, and after a certain amount of time, turn the wheel in the opposite direction to straighten the car. This constraint may increase the demands of the driving task compared to other artificial tasks that usually require a single motor movement. (2) In the real-world driving events, time is a critical factor, and slow RTs might cause accidents. Most driving tasks have an intrinsic time limitation, while most artificial tasks do not put any constraints on the participant's response times. This intrinsic time limitation may alter behavior in a natural setting compared to an artificial one. (3) In artificial dual-task experiments, none of the two tasks are intrinsically more important than the other one. In a dual-task paradigm, the main task is often the driving task, and the secondary task has less priority. This priority may also affect behavior in a dual-task paradigm. (4) The driving environment is a continuous environment that includes distracting elements in the scene, including the road and roadside elements, the movement in the scene caused by the interaction of the participant with the car, the car dashboard, odometer, and other car elements. These elements could alter behavior by either distracting the participants or facilitating the responses by providing an immersive experience. Most artificial tasks are discrete and contain isolated stimuli and a display that is not contingent upon the participants' responses. Considering these factors, in the current study, we designed a dual-task paradigm in a simulated driving environment to get one step closer to the real-world dual-task conditions. Although we are aware our paradigm does not replicate real-world driving, we think it has some of the main parameters of a lane change task in a driving situation. The first goal of this study is to measure the effect of SOA on the amount of dual-task interference in this paradigm and to examine the validity of dual-task theories in more naturalistic settings.

In most dual-task studies, the order of the presentation of the tasks has been kept fixed and predictable, and participants were explicitly instructed to perform the two tasks according to the order of the presentation. In contrast, task order is often random and unpredictable in real-world situations. One open question is whether the order of the response to the two tasks during driving is specified based on a first-come, first-served basis in which the order of the presentation determines the order of response, or a higher-order control mechanism determines this order.

In dual-task studies with simple designs (Sigman and Dehaene, 2005) in which the presentation order of the tasks is kept constant, and participants are often instructed to respond to the two tasks based on the presentation order, the first-come, first-served principle usually applies. However, recent studies which have made the order of the presentation of the two tasks unpredictable and have imposed no constraints for responding to the tasks according to the presentation order, support a higher-order control mechanism for managing the timing of the response to the two tasks (Sigman and Dehaene, 2006; Szameitat et al., 2006; Huestegge and Koch, 2010; Fernández et al., 2011; Leonhard, 2011). These studies have shown that increasing the perceptual difficulty of one of the tasks, such as degrading the stimulus, causes that task to be performed second (Sigman and Dehaene, 2006; Strobach et al., 2018; but see also Leonhard, 2011 for evidence on the contrary). Similarly, an increase in the difficulty of the decision (Fernández et al., 2011) or motor execution stages (Ruiz Fernández et al., 2013), causes participants to respond to that task later. These studies suggest that participants optimize the response order to decrease the total reaction time in dual-task conditions (Miller et al., 2009). All these studies have used simple artificial tasks rather than real-world naturalistic ones. It is still an open question if a higher-order control mechanism contributes to the response order in a naturalistic setting, such as a simulated driving environment. The second goal of this study was to measure the effect of task order predictability (OP) on the responses of the two tasks and the parameters of the DDM in naturalistic settings.

In sum, we aimed to investigate the underlying mechanism of dual-task interference in a simulated driving environment using drift-diffusion modeling. The paradigm consisted of a lane change task and an image discrimination task. We investigated the effect of SOA and the predictability of the order of the two tasks on the amount of dual-task interference. Using a DDM, we investigated whether the two tasks are processed in parallel or serially and how the predictability of the order of the two tasks influenced their processing. If the decision stages of the two tasks are processed serially, as predicted by the bottleneck theory, we expect the drift rate of the second task to be independent of SOA, and the non-decision time of the second task to be dependent on SOA. In contrast, if the decision stages of the two tasks are processed in parallel according to the predictions of the capacity sharing theory, we expect the drift rate of the second task to change and the non-decision time of the second task to not change across SOAs. Finally, if the decision stages of two tasks are processed in parallel, but there is some bottleneck in the process, as predicted by the hybrid model, we expect the drift rate and non-decision time of the second task to be dependent on SOA. These results will shed light on the underlying mechanisms of dual-task interference in more naturalistic settings.

MATERIALS AND METHODS

Participants

Twenty healthy, right-handed adults (11 females), aged 20–30, participated in the study. All participants had normal or corrected to normal vision. Additionally, all participants were not expert video game players, as defined by having less than 2 h of video-game usage per month in the past 2 years. All participants gave informed consent and were compensated for their participation.

Stimuli and Procedure

The dual-task paradigm consisted of a lane change driving task and an image discrimination task. The driving environment was designed in the Unity 3D game engine. Participants sat at a distance of 50 cm from a 22″ LG monitor with a refresh rate of 60 Hz and a resolution of 1,920 × 1,080 and responded to the tasks using a computer keyboard.

The driving environment consisted of a three-lane, desert road, without left/right turns or inclining/declining hills. Driving stimuli, composed of two rows of traffic cones (three cones in each row; **Figure 2A**), were presented on the two sides of one of the lanes in each trial, and the participants had to immediately redirect the car to the lane with the cones and pass through the cones. The space between the two rows of cones was such that the car could easily pass through them without collision. The cones were always presented in the lanes immediately to the left or immediately to the right of the car's lane so that the participants had to change only one lane per trial. The lane change was done gradually: the participant had to hold the corresponding key to direct the car in between the two rows of cones, and then release the key when the car was situated correctly. Any early or late key press or release would cause a collision with the cones and a performance loss in that trial. The fixation cross was jittered for 100 ms to provide online feedback in case of a collision with the traffic cones. The participants were instructed not to change lane before the cones appeared. Trials in which participants changed lane before the presentation of the cones were considered false and removed from the analysis. Using this method, we could divide a continuous driving task into individual trials with predetermined onset and ends. At the beginning of the block, participants speeded up to 80 km/h using the "up" arrow key with the middle finger of the right hand. During the block, the speed was kept constant, and the lane change was performed by pressing the right and left arrow with the middle and index fingers of their right hand, respectively. For the image discrimination task, a single image of either a scene

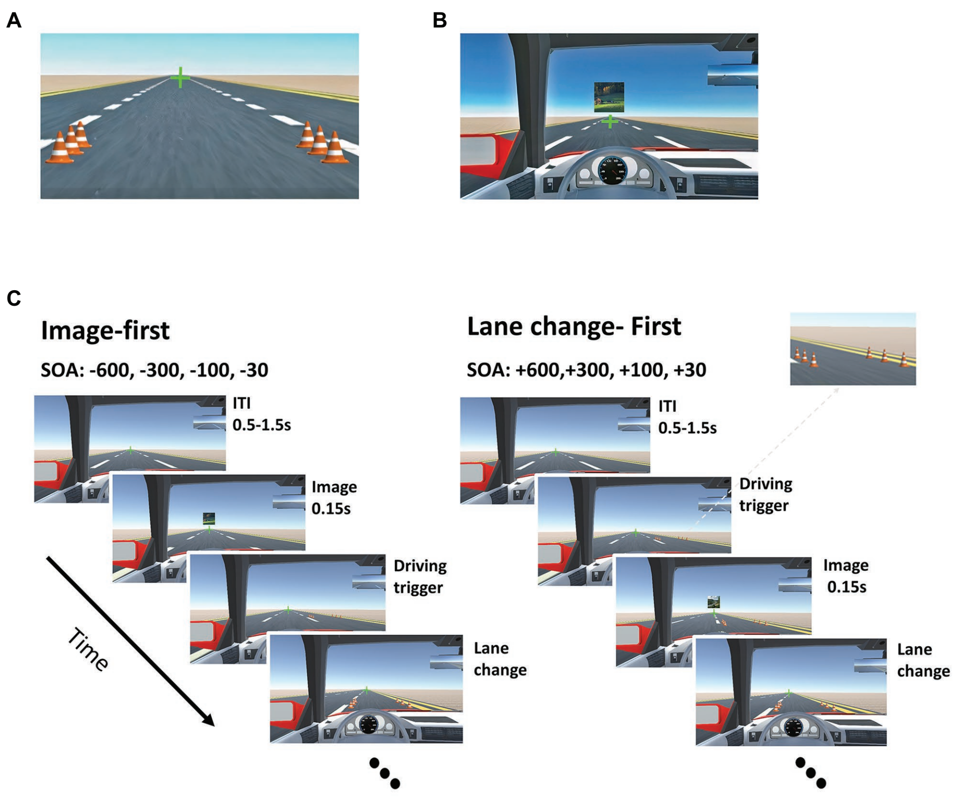

FIGURE 2 | Dual-task paradigm. **(A)** A sample display showing the driving stimulus consisting of two rows of traffic cones in the middle driving lane. The cones were randomly presented in each lane, and participants had to drive through them without collision. **(B)** A sample display showing an image discrimination presented above the fixation point. Participants determined if the image was a face or a scene. **(C)** The sequence of events for a sample trial in which the image task was presented first (left), and another in which the driving task was presented first (right). The inter-trial interval (ITI) varied between 0.5 and 1.5 s. The image lasted for 150 ms, and the cones were presented 30, 100, 300, or 600 before or after the image. Participants had to perform a lane change immediately after the appearance of the cones, and an image discrimination task immediately after the presentation of the image.

or a face was presented for 150 milliseconds centered at 2° eccentricity above the fixation cross (**Figure 2B**). The size of the image was 2.5° of visual angle. Participants pressed the "*x*" and "*z*" keys on the computer keyboard with the middle and index fingers of their left hand to determine whether the image was a face or a scene, respectively. The images were pseudo-randomly selected from a set of 864 images of scenes and 435 images of faces. We selected only natural scenes and neutral faces. If participants responded incorrectly, the green fixation cross turned red, and if they responded late, it turned orange for 100 ms. The length of each trial was 3 s, and the inter-trial interval varied randomly from 0.5 to 1.5 s. For the first trial in each block, the onset of the trial was set to 2 s after the beginning of the block. The end of the trial was set to when the rear end of the car reached the end of the set of traffic cones.

The experiment consisted of two different conditions: (1) "Predictable" task order condition, and (2) "Unpredictable" task order condition. In two experimental conditions, the two tasks were presented with eight possible SOAs (−600, −300, −100, −30, +30, +100, +300 and +600 ms). In the negative SOAs, the image discrimination was presented first (image-first, **Figure 2C**), and in the positive SOAs, the lane change was presented first (lane change-first, **Figure 2C**). In the Predictable conditions, the order of the presentation was fixed, so that in two of the four blocks, the driving task was presented first, and in the other two, the image discrimination task was presented first. In the Unpredictable condition, the order of the presentation of the two tasks was not predictable in each trial. Trials with driving as the first task were interleaved with trials with the image discrimination as the first task. Before the start of each block, participants were informed about the type of the block.

In addition to the dual-task conditions, participants performed two single-task conditions: (1) single driving task and (2) single image discrimination task. In the single-task conditions, both the lane change and image stimuli were presented, but the participant only responded to one of them, ignoring the other. In the single image discrimination condition, the driving was on autopilot, and participants only responded to the images. In the single lane change condition, participants performed the lane change task and ignored the images.

Participants were told to focus on the fixation cross at the center of the page and respond to each task as fast as possible.

At the end of each block, participants were informed about their performance on each task as well as their total performance. The performance in the driving task was calculated as the percentage of trials in which the participant passed through the cones without collision. The performance in the image discrimination task was calculated as the percentage of correct identifications.

Participants completed four blocks of 64 trials for each dual-task condition and two blocks of 32 trials for each single-task condition. There was a 1-min interval between blocks and a 5-min break after finishing all the blocks in each condition. The order of the blocks was counterbalanced across participants.

Before performing the main experiment, all participants performed a block of 20 trials for every single-task. If their accuracy was 80% or higher, they proceeded to the main experimental blocks. Otherwise, they repeated blocks of 40 trials for each task until they reached 80% accuracy. After the single-task training, participants performed the dual-task training block. The dual-task training was similar to the single-task training block, with the difference that if after 20 trials, the dual-task performance did not reach the 75% threshold, the training was repeated with blocks of 50 trials.

Drift Diffusion Model Fitting

To investigate if the two tasks were processed serially, or in parallel we used a DDM in which each trial was modeled as a combination of a non-decision time and a decision time consisting of a random drift towards decision bound (**Figure 1**). Model parameters consisted of: (1) parameter z denoting the starting point of the decision process, (2) parameter a denoting the decision threshold, (3) parameter v representing the speed of information accumulation or drift rate, and (4) parameter $t0$ denoting the non-decision time pertaining to the combination of all other times in the trial excluding the drift-diffusion time. The DDM was implemented in the current study, by fitting the parameters z, a, v, and $t0$. We modified the DDM, so that z and a were independent of SOA, and v and $t0$ were dependent on SOA. Therefore, in the modified DDM, four values were fit for the parameter v and four values for the parameter $t0$ corresponding to the four SOAs, one value for the parameter a and one value for the parameter z across all SOAs.

We used the Fast-dm package, developed by Voss and Voss (2007), for model fitting. Fast-dm is a package for fast drift-diffusion modeling. This package uses a partial differential equation method and a simplex routine to obtain the parameters of the DDM, and uses the calculated cumulative density function (CDF) of the predicted RTs to estimate the goodness of fit using a Kolmogorov-Smirnov (KS) function (Voss and Voss, 2008; Voss et al., 2015). The DDM was fit separately for each task (lane change/image discrimination task) and each participant. We also calculated R^2 values as an additional measure to examine the goodness of fit of the model.

Data Analysis

Only the correct trials were used for the RT analysis. In the dual-task conditions, if the response to both tasks was correct, that trial was included in the analysis. The trials in which the reaction time to each of the tasks was <200 ms and >1,500 ms were excluded from the analysis (3.48% of the trials). To quantify the effect of SOA on RTs and DDM parameters, one-way repeated-measures ANOVAs were used and to quantify the effect of SOA and task conditions on RTs, accuracies, and DDM parameters, two-way repeated-measures ANOVAs were used. A Greenhouse-Geisser correction was performed when sphericity had been violated. To compare the threshold, slope, and shift of the logistic regression function between the two task conditions, a paired t-test was used. We also performed three-way repeated measure ANOVAs with task condition, task order and SOA as three factors. The details of the statistical results are placed in **Supplementary Tables S1–S3**. In addition, we used t-test to statistically compare RTs, accuracies and DDM parameters between task conditions (dual vs. single/predictable vs. unpredictable) for each SOA. The details of the statistical tests for this analysis are placed in **Supplementary Tables S7–S9**. False Discovery Rate correction (Benjamini and Hochberg, 1995) was applied in all cases that multiple comparisons were performed.

We used a logistic regression model to examine the effect of SOA and OP on the order of the response of the two tasks. The probability that the lane change response was initiated before the image discrimination response was determined by the following formula:

$$\text{Logit}\ [\text{P}] = \beta_0 + \beta_1 \text{C}$$

where P stands for the probability that the lane change task was responded to first and C stands for SOAs. Parameters β_0 and β_1 were calculated for each participant. The model was fit separately on the data from the two dual-task conditions. A maximum likelihood estimation procedure was used for curve fitting.

RESULTS

Effect of Dual-Task Interference on RTs

We first focused our analysis on the dual-task condition with the predictable task order and compared it with the single-task conditions (**Figure 3**). We ran four two-way repeated-measures ANOVAs with task condition (dual/single), and SOA as factors separately for the lane change and the image discrimination and the lane change-first and image-first task orders. **Table 1** contains the details of the statistical results. Results showed a significant main effect of task condition with longer RTs in the dual- compared to the single-task condition in all cases [$Fs(1,19) > 6.21$, $ps < 0.023$, $\eta_p^2 > 0.24$]. The effect of SOA was significant in all cases [$Fs(3,57) > 6.5$, $ps < 0.006$, $\eta_p^2 > 0.25$] except for the lane change RTs in the lane change-first task order [$F(1.49, 26.84) = 2.55$, $p = 0.099$, $\eta_p^2 = 0.11$]. The interaction between task condition and SOA was also significant in all cases [$Fs(1,57) > 3.05$, $ps < 0.041$, $\eta_p^2 > 0.13$]. Further comparisons looking at the effect of SOA on RTs in the dual-task condition using one-way repeated-measures ANOVAs showed a significant effect of SOA on the RTs in all cases [$Fs(3,57) > 3.95$, $ps < 0.015$, $\eta_p^2 > 0.17$] except for the lane change when it was presented first [$F(1.6, 28.95) = 2.55$, $p = 0.49$, $\eta_p^2 = 0.02$]. Consistent with previous studies of

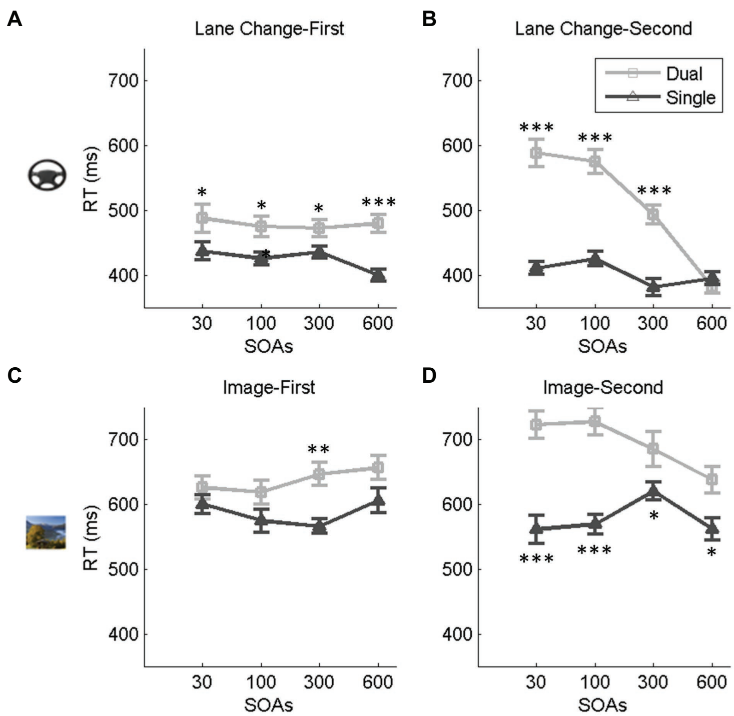

FIGURE 3 | Effect of task condition (dual vs. single) and SOA on RTs. **(A,B)** These panels indicate the RTs for the lane change in the lane change-first and lane change-second task orders, respectively, for the single-task (red) and the dual-task (blue) conditions. **(C,D)** These panels show the image discrimination RTs in the single (red) and the dual (blue) task conditions for the image-first and the image-second task orders, respectively. In all panels, errorbars show standard errors of mean and stars show a significant difference between task conditions for each SOA (* < 0.05, ** < 0.01, and *** < 0.001).

TABLE 1 | Results of two-way repeated-measure ANOVAs for the effect of task condition (dual vs. single), SOA, the interaction between the two on RTs, and SOA in dual shows the results of one-way repeated-measures ANOVAs for the effect of SOA on RTs separately in the dual-task condition.

		Lane change-first	Lane change-second	Image-first	Image-second
Task condition (dual vs. single)	*F*	10.19	43.10	6.22	23.20
	df	1, 19	1, 19	1, 19	1, 19
	p	**0.005**	**0.002**	**0.022**	**<0.0001**
	η_p^2	0.349	0.694	0.247	0.550
SOA	*F*	2.55	101.60	7.29	6.56
	df	1.49, 26*	3, 57	3, 57	1.8, 39*
	p	0.099	**0.0002**	**0.0002**	**0.005**
	η_p^2	0.119	0.843	0.277	0.257
Task condition × SOA	*F*	3.05	48.24	3.24	6.99
	df	3, 54	1.57, 29*	3, 57	3, 57
	p	**0.036**	**0.002**	**0.041**	**0.002**
	η_p^2	0.138	0.717	0.146	0.269
SOA in dual	*F*	0.657	103.7	7.10	8.35
	df	1.60, 28*	1.43, 27*	3, 57	1.61, 31*
	p	0.491	**0.002**	**0.002**	**0.002**
	η_p^2	0.023	0.845	0.272	0.305

All p-values were corrected for multiple comparisons, and Greenhouse-Geisser correction was done when necessary (indicated by a star). The significant p-values were shown in bold.

dual-task interference (Pashler and Johnston, 1989; Tombu and Jolicoeur, 2002; Sigman and Dehaene, 2005), when the image discrimination or the lane change tasks were presented second, the RTs increased at shorter SOAs. Interestingly, when the image discrimination was presented first, decreasing SOAs had an opposite effect, with shorter SOAs showing faster RTs. These results have not been observed in previous dual-task studies and might be driven by participant's urge to finish the image discrimination task sooner in order to reduce the interference on driving.

Further analysis showed that the image discrimination RTs were generally longer than the lane change task RTs

(**Supplementary Figure S3**), but the magnitude of the dual-task effect was not different between the tasks (for more details see **Supplementary Table S6**). We also investigated if the image type (scenes vs. faces) affected RTs. Results showed no significant difference between scene image RTs and face image RTs [$t(159) = 1.13$, $p = 0.11$]. Also, the lance change RTs did not change in trials in which the image was a scene compared to those in which it was a face [$t(159) = 1.57$, $p = 0.118$].

We also calculated the accuracy of participants in single- and dual-task conditions. Results showed that the accuracies were above 95 and 90% for all conditions of the lane change task and the image discrimination task, respectively (**Supplementary Figures S1**, **S2**).

In sum, our results show a clear effect of SOA on driving and image discrimination RTs. The presence of these strong effects allows us to use SOA as a factor for drift-diffusion modeling in the next section to investigate the nature of dual-task interference in our simulated driving set up.

Drift-Diffusion Modeling of the Effect of Dual-Task Interference on RTs

Drift diffusion modeling was used to investigate if a change in SOA affects the drift rate, non-decision time, or both. The model could account for most of the variance in the data (R^2: Lane change-first 0.78 ± 0.03, Lane change-second 0.94 ± 0.02, Image-first 0.71 ± 0.04, and Image-second 0.84 ± 0.03), and the distribution of the RTs from the model fit was not significantly different from the original data in all subjects and all conditions ($ps > 0.1$).

Next, we investigated the effect of SOA on the two model parameters *v* and *t0*, corresponding to the drift rate and non-decision times. Serial processing of the two tasks would lead to an increase in the *t0* for the second task, while parallel processing of the two tasks would decrease the *v* for the second task at shorter SOAs. Results showed that when either of the two tasks was presented second, *v* decreased and *t0* increased at shorter SOAs [$Fs(3,57) > 6.66$, $ps < 0.003$, $\eta_p^2 > 0.29$; **Figures 4B,D,F,H**]. No significant change in *v* or *t0* was observed when driving was presented first ($p > 0.05$; **Figures 4A,E**) and a decrease in both *t0* and *v* was observed at shorter SOAs when the image discrimination was presented first [$Fs(3,57) > 3.94$, $ps < 0.023$, $\eta_p^2 > 0.17$; **Figures 4C,G**]. The details of statistical tests are shown in **Table 2**. These results suggest that the two tasks are neither processed in a strictly parallel nor a strictly serial manner, as a change in the non-decision time is always accompanied by a change in the drift rate.

Effect of Task OP on RTs

To investigate the effect of task OP on the RTs during dual-task performance, we compared the main dual-task condition in which the task orders were predictable (i.e., the two task orders were presented in separate blocks) to a condition in which the task orders were unpredictable and varied randomly from trial to trial within a block. We ran four two-way

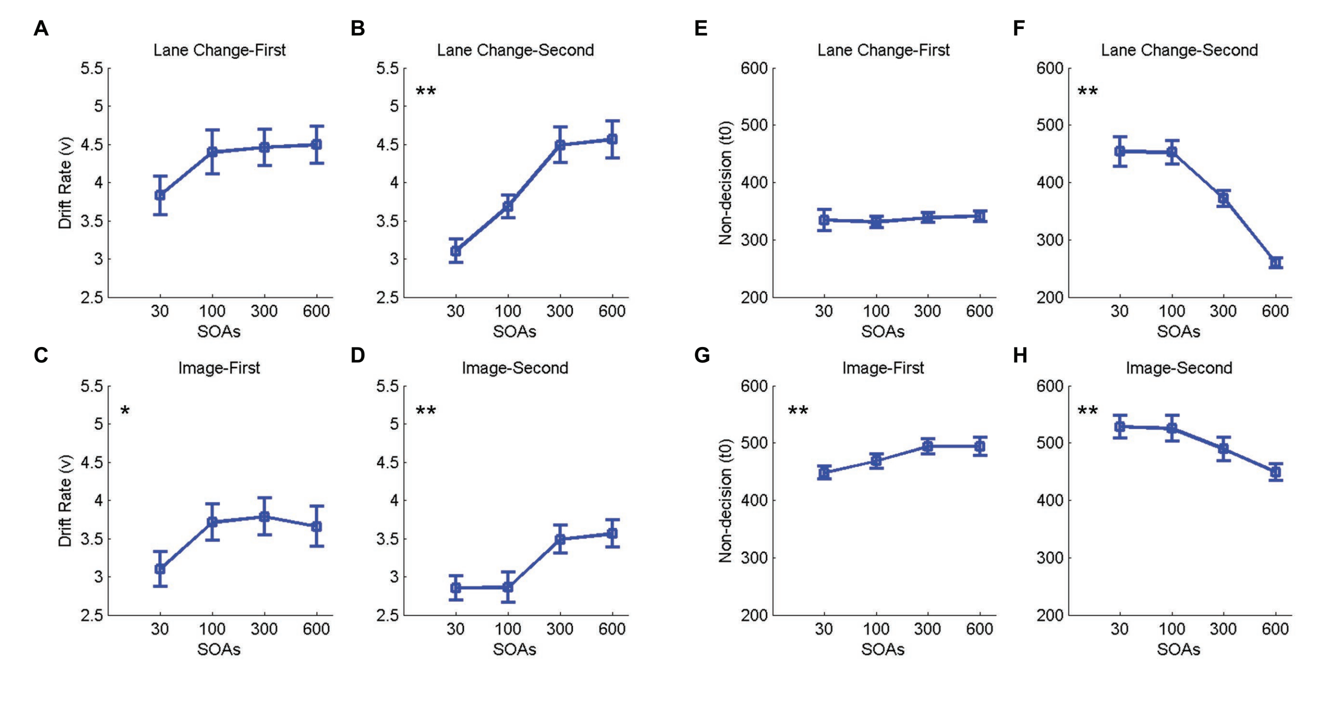

FIGURE 4 | Effect of SOA on drift rates (*v*) and non-decision times (*t0*). Panels **(A–D)** on the left show the effect of SOA on the drift rate (*v*) for lane change in the lane change-first **(A)** and lane change-second **(B)** conditions and that for the image discrimination in the image-first **(C)**, and image-second **(D)** conditions. Panels **(E–H)** on the right show the effect of SOA on non-decision time (*t0*) for lane change task in the lane change-first **(E)** and lane change-second **(F)** conditions and that for the image discrimination task in the image-first **(G)** and image-second **(H)** conditions. In all panels, errorbars show standard errors of mean and stars show a significant effect of SOA (* < 0.05 and ** < 0.01).

TABLE 2 | One-way repeated-measures ANOVAs for the effect of SOA on *v* and *t0*.

		Lane change-first		Lane change-second		Image-first		Image-second	
		v	*t0*	*v*	*t0*	*v*	*t0*	*v*	*t0*
SOA	*F*	1.59	3.46	15.03	64.42	3.95	7.96	6.67	12.20
	df	1.87, 35.53*	1.60, 30.43*	3, 57	1.59, 30.37*	3, 57	1.35, 25.80*	3, 57	1.86, 35.36*
	p	0.217	0.663	**0.002**	**0.001**	**0.022**	**0.006**	**0.002**	**0.001**
	η_p^2	0.078	0.018	0.442	0.772	0.172	0.295	0.296	0.391

All p-values were corrected for multiple comparisons and Greenhouse-Geisser correction was done when necessary (indicated by a star). The significant p-values are shown in bold.

TABLE 3 | Results of two-way repeated-measures ANOVAs for the effect of OP and SOA on RTs and one-way repeated-measures ANOVAs for effect SOA on RTs in the unpredictable condition.

		Lane change-first	Lane change-second	Image-first	Image-second
Task condition (predictable vs. unpredictable)	*F*	10.21	11.81	3.53	4.29
	df	1, 19	1, 19	1, 19	1, 19
	p	**0.005**	**0.012**	0.076	0.069
	η_p^2	0.350	0.383	0.157	0.184
SOA	*F*	2.83	88.89	3.35	7.55
	df	1.48, 28*	1.51, 28*	3, 57	1.65, 31*
	p	0.089	**0.0004**	**0.050**	**0.006**
	η_p^2	0.130	0.824	0.150	0.285
Task condition × SOA	*F*	5.02	7.06	3.37	3.07
	df	3, 57	3, 57	3, 57	1.83, 34*
	p	**0.003**	**0.004**	**0.041**	0.057
	η_p^2	0.215	0.271	0.151	0.139

All p-values were corrected for multiple comparison and Greenhouse-Geisser correction was done when necessary (indicated by a star). The significant p-values are shown in bold.

TABLE 4 | Results of two-way repeated-measures ANOVAs for the effect of OP and SOA on *v* and *t0*.

		Lane change-first		Lane change-second		Image-first		Image-second	
		v	*t0*	*v*	*t0*	*v*	*t0*	*v*	*t0*
OP	*F*	4.02	3.06	0.283	11.27	0.891	0.019	0.002	5.07
	df	1, 19	1, 19	1, 19	1, 19	1, 19	1, 19	1, 19	1, 19
	p	0.236	0.128	0.801	**0.012**	0.714	0.893	0.968	**0.052**
	η_p^2	0.175	0.139	0.015	0.372	0.045	0.001	0.001	0.211
SOA	*F*	2.10	1.33	28.02	43.23	7.23	9.03	3.45	5.93
	df	1.74, 33*	1.44, 27*	3, 57	1.40, 26*	3, 57	1.73, 32*	3, 57	1.93, 36*
	p	0.143	0.319	**0.002**	**0.002**	**0.002**	**0.002**	**0.036**	**0.008**
	η_p^2	0.100	0.056	0.596	0.695	0.276	0.322	0.157	0.238
OP × SOA	*F*	1.78	3.21	1.37	10.91	2.16	1.84	3.50	1.62
	df	3, 57	1.87, 35*	2.09, 39*	3, 57	3, 57	2.07, 39*	3, 57	2.19, 41*
	p	0.188	0.110	0.188	**0.003**	0.188	0.208	0.112	0.208
	η_p^2	0.086	0.145	0.084	0.365	0.100	0.089	0.156	0.079

All p-values were corrected for multiple comparisons and Greenhouse-Geisser correction was done when necessary (indicated by a star). The significant p-values are shown in bold.

repeated-measures ANOVAs with task condition (predictable/unpredictable) and SOA as the two factors, separately for the lane change and the image discrimination, and the lane change-first and image-first task orders. The details of the statistical tests are summarized in **Table 3**. The effects of OP, SOA, and their interaction on RTs were significant in both lane change-first and lane change-second conditions [$Fs > 5.03$, $ps < 0.013$, $\eta_p^2 > 0.21$; **Figures 5A,B**] except for the effect SOA on the lane change-first that was marginally significant [$F(1.48,28) = 2.83$, p = 0.089, $\eta_p^2 = 0.13$]. When the image discrimination was presented first (**Figure 5C**), OP had a marginally significant effect on mean image discrimination RTs [$F(1,19) = 3.54$, $ps = 0.076$, $\eta_p^2 = 0.15$], and the interaction between OP and SOA was significant [$F(3,57) = 3.37$, $ps < 0.041$, $\eta_p^2 > 0.15$]. When the image discrimination was presented second (**Figure 5D**), the effect of OP on RTs [$F(1,19) = 4.29$, $ps = 0.069$, $\eta_p^2 = 0.18$], and the interaction between OP and SOA on RTs [$F(3,57) = 3.07$, $ps = 0.057$, $\eta_p^2 = 0.13$] were marginally significant.

Furthermore, we investigated the effect of SOA separately in the unpredictable conditions using one-way repeated-measures ANOVAs (note that the effects for the predictable condition

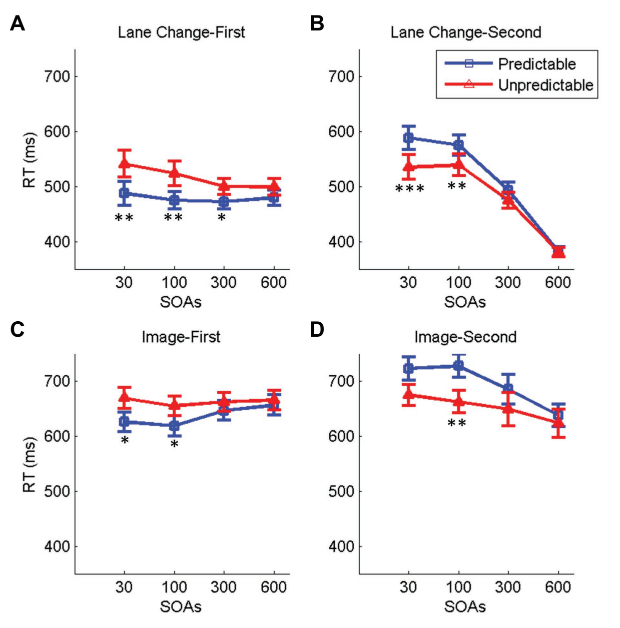

FIGURE 5 | Effect of OP and SOA on RTs. The two top panels show the RTs for the lane change in the lane change-first **(A)** and lane change-second **(B)** task orders for the predictable (blue) and the unpredictable (red) task order conditions. The two bottom panels show the RTs for the image discrimination task in the image-first **(C)** and image-second **(D)** task orders for the predictable (blue) and the unpredictable (red) task order conditions In all panels, error bars show standard errors of mean and stars show a significant difference between task conditions for each SOA (* < 0.05, ** < 0.01, and *** < 0.005).

are already reported in the previous section). The results showed a significant effect of SOA on the RTs in all cases [$Fs(3,57) > 3.75$, $ps < 0.015$, $\eta_p^2 > 0.16$] except for when the image discrimination was presented first [$Fs(3,57) = 0.62$, $ps < 0.52$, $\eta_p^2 > 0.03$].

In general, these results demonstrate that OP increases the mean RT of the first task and decreases the mean RT of the second task with the changes more pronounced when the tasks get closer together in time. These results show that unpredictability of the task order attenuates the effect of SOA on RTs for all cases except the lane change-first RTs. We next investigated the possible origin of this attenuation effect.

Effect of Task OP on the Response Order

To investigate the effect of SOA and OP on the order of the response to the two tasks, we calculated the probability that the lane change task was responded to first in each SOA and for each subject (**Figure 6A**) and fit a logistic regression model to these probability values. The model was fit separately for each of the two dual-task conditions, and an intercept (β_0 in the logistic model described in the methods) and a slope (β_1 in the logistic model) was calculated for each condition and each participant. We also calculated the SOA value in which the probability of responding to the lane change task first was 50% (T50). Then, to quantify the effect of OP on the response order, the model outputs and the T50 value across the two experimental conditions were submitted to a paired t-test. OP had no significant effect on the shift (β_1) of the logistic function [$t(1,19) = 0.323$ $p = 0.75$; **Figure 6B**]. The slope of the logistic function (β_1) was significantly influenced by OP [$t(1,19) = 3.08$, $p = 0.006$]. Negative T50 values in both conditions show that participants had a general bias to respond to the lane change task first (**Figure 6C**) but this bias was the same across the two conditions [$t(1, 19) = 0.317$, $p = 0.75$]. At SOA = 0, in more than 60% of trials lane change was responded to first. In sum, these results showed that OP changes the response order to the two tasks and has no effect on the bias in favor of the lane change task.

Drift-Diffusion Modeling of the Effect of Task OP on RTs

Drift Diffusion Model (DDM) was fit to the data from the predictable and unpredictable task order conditions, separately, and output model parameters were compared for the two conditions. The results of model fitting on the unpredictable task order condition showed that the model could account for most of the variance in the data (R^2: lane change-first 0.70 ± 0.04, lane change-second 0.96 ± 0.01, image-first 0.75 ± 0.03 and image-second 0.82 ± 0.03) and the distribution of the RTs from the model fit was not significantly different from that of the original data in all subjects and all conditions ($ps > 0.09$). We ran two-way repeated-measures ANOVAs to investigate the effect of task condition (Predictable vs. Unpredictable) and SOA on the two parameters *t0* and *v*, separately for the two task orders, and the lane change and the image discrimination tasks. The details of the statistical test are shown in **Table 4**. The effect of OP on *v* was not significant in all cases ($ps > 0.05$; **Figures 7A–D**). This effect on *t0* was only significant in the lane change-second [$F(1,19) = 11.27$, $p = 0.012$, $\eta_p^2 = 0.37$; **Figure 7F**] and marginally significant for image-second conditions [$F(1,19) = 5.07$, $p = 0.052$, $\eta_p^2 = 0.21$; **Figure 7H**] and was not significant in the lane change-first and image-first conditions ($ps > 0.05$; **Figures 7E,G**). SOA had a significant effect on *v* and *t0* in all conditions [$F(3,57) > 3.54$, $p < 0.02$, $\eta_p^2 > 0.15$], except when the lane change task was presented first ($p > 0.05$; **Figure 7A**). The interaction of OP and SOA on *t0* was only significant for lane change-second conditions [$F(3,57) = 10.91$, $p = 0.003$, $\eta_p^2 = 0.36$; **Figure 7F**]. These results show that when either the image discrimination or the lane change tasks were presented second, unpredictability changed the non-decision time of the tasks. Note that the analysis of the response order showed that in the unpredictable condition, the second task was more likely to be responded to first. The changes in the order of response could be tightly related to the decrease in the non-decision time of the second task.

DISCUSSION

The purpose of this study was to investigate the underlying mechanisms of dual-task interference in a simulated lane change environment. We used a systematically controlled dual-task

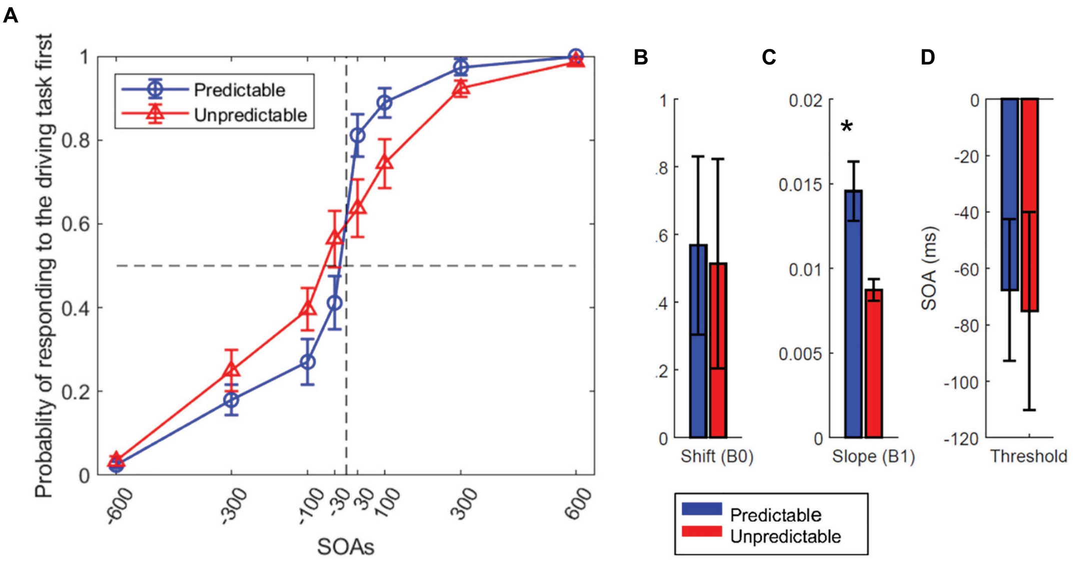

FIGURE 6 | Effect of OP on the response order. Predictable and Unpredictable conditions are shown in blue and red colors, respectively. **(A)** The probability of first responding to the lane change task plotted for the two task conditions. The curves are fit to the average data using a logistic regression function. **(B)** The shift of the logistic regression function (β_0), **(C)** the slope of the logistic function (β_1), and **(D)** The T50 (the SOA in which participants responded to the lane change task first with 50% probability), for the predictable (blue) and unpredictable (red) conditions. The shift did not differ between the two conditions, but the slope was shallower in the unpredictable condition ($p < 0.006$). There was a general bias for responding to the lane change task first in both conditions. In all panels, error bars show standard errors of mean. The star shows a significant difference between task conditions (* < 0.05).

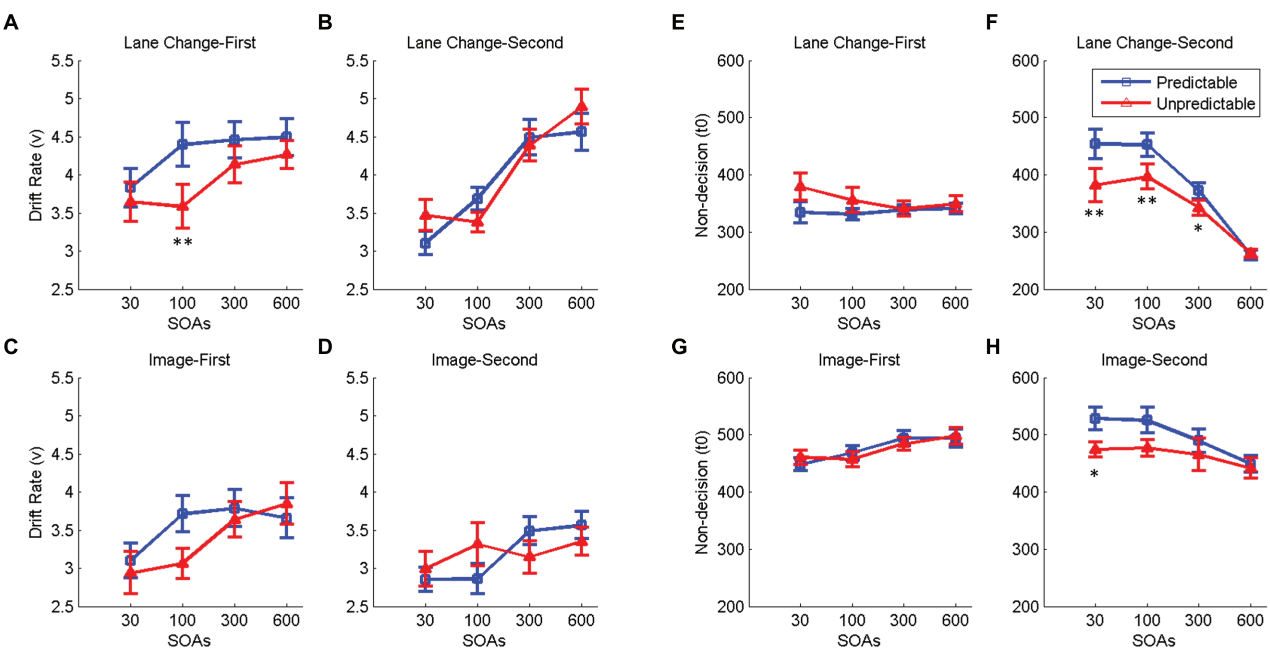

FIGURE 7 | Effect of OP and SOA on drift rates (*v*) and non-decision times (*t0*). Blue lines and red lines show the predictable and unpredictable task orders, respectively. Panels **(A–D)** on the left show the effect of OP and SOA on the drift rate (*v*) for lane change in the lane change-first **(A)** and lane change-second **(B)** conditions and that for the image discrimination in the image-first **(C)** and image-second **(D)** conditions. Panels **(E–H)** on the right show the effect of OP and SOA on non-decision time (*t0*) for lane change in the lane change-first **(E)** and lane change-second **(F)** conditions and that for the image discrimination task in the image-first **(G)** and image-second **(H)** conditions. In all panels, errorbars show standard errors of mean and stars show a significant difference between task conditions for each SOA (* < 0.05 and ** < 0.01).

paradigm in which an image task was presented at set times before or after the lane change task. We investigated the effect of dual-task, SOA, and unpredictability of task order on subjects' performance and modeled the results using a DDM. Results showed strong dual-task effects on both tasks with stronger effects at shorter SOAs for the second tasks. DDM showed a change in both the drift rate and non-decision times, suggesting that a hybrid model containing features of both serial and parallel processing best accounts for the results. Unpredictability of the task order attenuated the effect of SOA by changing the order of the response to the two tasks. This effect induced a change in the non-decision time of the second task in the DDM.

The observation of a strong dual-task effect on both image discrimination and lane change RTs when they were presented second is compatible with the predictions of both capacity sharing and bottleneck theories. But our behavioral results are not fully compatible with either of the two theories. We observed a clear dual-task effect comparing the RTs of the single-task with the dual-task conditions when the tasks were presented first with longer RTs for the single-compared to the dual-task condition, and a decrease of RT at shorter SOAs for the image task. The bottleneck theory predicts no change in the RT in the single-compared to the dual-task, and the capacity sharing theory predicts an RT effect that increases at shorter SOAs. Our observations are different from those reported by Levy et al. (2006) and Hibberd et al. (2013) who only observed a dual-task effect for the second task in a simulated driving environment. In these two studies, for the driving task, participants performed a car following in which they pressed the brake pedal when the color of the brake light changed. In our study, for performing the driving, participants had to press a key, hold it, and tune the location of the car to avoid the collision. The more continuous and multi-step nature of the response in our study might have increased the time pressure and demands of the driving task, imposing a priority for processing it. This increased priority, in turn, may have caused the participant to not invest all their resources on the image task when they knew that a driving trigger may be presented soon. The increased priority may have also caused participants to try to respond to the first-presented image task faster at shorter SOAs to release resources for the driving task. These effects clearly suggest a more complex management of resources than what is suggested by the bottleneck or capacity sharing theories.

Results of our DDM analysis further confirm that neither the bottleneck theory with its prediction of a strictly serial processing of tasks nor the capacity sharing theory with predictions of a fully parallel processing can account for our results. This is because both the drift rate and the non-decision times of the second tasks are found to be modulated across SOAs. This result suggests some degree of capacity sharing for the processing of the two tasks. In addition, they suggest some delay in the processing of the second task due to a potential bottleneck. In other words, our results suggest that the best model to account for dual-task interference in driving is a hybrid model combining the two extremes suggested by capacity sharing and bottleneck theories. Zylberberg et al. (2012) modeled RT of the second task with a term for accumulation time that includes the time from stimulus onset to end of the decision process and a term for the post-accumulation time that includes the time from the end of the decision process to the motor response. Their results showed that both accumulation and post-accumulation times increase in short compared to the long SOA conditions. These results are compatible with a hybrid model as they show that the dual-task interference decreases the efficacy of evidence accumulation without halting it and causes a delay in mapping the decision to motor response. In line with Zylberberg et al. (2012), the result of the current study demonstrates that the decision stage of the second task is processed in parallel with the decision stage of the first task, and there is also some bottleneck in processing the second task. In our DDM modeling, it is not possible to determine if the bottleneck is before or after the evidence accumulation stage. It is plausible that the mapping of the decision to the motor output happens in a serial manner, and this imposes a bottleneck on the production of the response, but proof of this point requires further studies.

Results of our task order predictability manipulation suggest the involvement of an active higher order control mechanism for scheduling the tasks (De Jong, 1995; Luria and Meiran, 2003; Sigman and Dehaene, 2006; Szameitat et al., 2006; Fernández et al., 2011; Leonhard, 2011; Ruiz Fernández et al., 2013) as opposed to passive scheduling of the tasks on a first-come first-served basis (Pashler, 1994b; Bunge et al., 2000; Jiang, 2004). A passive scheduling account would predict no effect of task order predictability on response orders while in our experiment, task order predictability changed the order of the response to the two tasks causing the RTs for the first task to increase and those for the second task to decrease. Our results do not fully replicate previous studies of task order predictability in simple artificial dual-tasks (Sigman and Dehaene, 2006; Töllner et al., 2012). These studies report an increase in RT for both the first and second tasks. However, unlike our paradigm these studies have instructed the participants to respond to the stimuli according to the presentation order. Imposing this artificial response order may have increased the dual-task costs leading to longer RTs (Strobach et al., 2018). Our paradigm is closer to naturalistic settings in which the secondary task can happen at any time relative to the driving event and are more applicable to natural settings.

Another feature of our data also favors an active account of task scheduling. Participants had an overall bias to respond to the lane change task first. Order predictability had no effect on this average bias. This bias might be due to the context of the lane change task and the intrinsic time pressure for responding to the lane change task in order to avoid collision with the cone obstacles. It may also be related to the differences in the difficulties between the image and lane change tasks. Miller et al. (2009) have suggested an RT optimization model for scheduling of tasks in dual-task paradigm. This model suggests that the participants' aim in a dual-task paradigm is to decrease the total RT (RT of the first task + RT of the second task). Therefore, they tend to respond to the easy task sooner than the difficult one. In other words, the duration of the components of the two tasks determines which task is responded to first (see Sigman and Dehaene, 2006 and Fernández et al., 2011 and Ruiz Fernández et al., 2013 for evidence in favor of this model). It is hard to evaluate if our results favor this model or not. In our paradigm, the decision time and non-decision times of the images task were slightly longer, while the motor stage of the lane change task was likely more difficult as it involved a series of motor movements. It is hard to speculate about the effect of each of these stages on the decision for task order without further experiments manipulating each stage in isolation. Regardless of the underlying reason, the prioritization of the lane change task over the image task shows that the order of the presentation of the tasks does not dictate the order of the processing.

Studies of working memory have categorized executive functions into distinct components (Jonides et al., 2008; Nee et al., 2013). These include shifting attention between items in working memory, updating the actively maintained items, and preventing interference from outside distractors and internal intrusions (Courtney et al., 2007; Bledowski et al., 2009; Nee et al., 2013). We did not have an explicit working memory task, but our behavioral and modeling results, in line with previous findings (De Jong, 1995; Meyer and Kieras, 1997; Szameitat et al., 2002; Piai and Roelofs, 2013) suggest that similar executive functions may be at play in our dual-task paradigm to coordinate which task should be prioritized and processed first, to divide the resources during the evidence accumulation of the two tasks, and to maintain the information of one task during the (possibly post-accumulation) bottleneck until the process of the other task is completed. Based on our results, we can speculate that resources are divided between tasks with a general preference for the first task and an additional preference for the lane change task. The information is then updated and maintained for the two tasks during the evidence accumulation and response selection phases, with the first task imposing constraints and interfering with the process of the second task.

We have used the broad term of interference for the phenomenon of performance decline and changes in the parameter of DDM in our dual-task paradigm. This term has been used in the literature to describe multiple distinct phenomena (Pashler, 1994a; Luck, 1998; Marois and Ivanoff, 2005; Johnston and McCann, 2006; Tombu et al., 2011), including performance declines due to internal processes and those related to distractions from external stimuli. In a dual-task paradigm, when the first task is being processed, the presence of the stimulus of the second task could serve as an external distractor. Once the process of the second task starts, the information from the second task is no longer an external distractor. The effect of this external distraction can be observed in our control single-task conditions, as in this condition, the stimuli for the ignored task are still present. Small modulations in the RTs in the single-task condition are possibly related to external distraction from the ignored task. The dual-task effect, however, is much stronger than this small modulation. This dual-task effect, observed especially in the second task, is due to proactive interference (Jonides and Nee, 2006) from the internal processing of the first task imposing a reduction in the drift-diffusion rates of the second task. Other than this interference, task shifting may play some roles in our increased RTs. As discussed above, the changes in the non-decision time could be related to the shift between the two tasks during the post-accumulation phase (Zylberberg et al., 2012).

Our simulated driving paradigm was close to a real-life driving task in some respects such as having a continuous driving scene with a multi-lane road and a car dashboard and requiring a two-step response (pressing and releasing the button at prompt times) with an intrinsic time pressure for the driving task. But our paradigm also kept the driving task and driving environment as simple as possible to control the main experiment variables systematically. Participants drove at a constant speed in a high-way desert with no hill or turn, and other cars in our paradigm. The display was viewed on a 2D computer screen as opposed to a 3D environment. The responses were collected using button presses. Participants were only focused on the lane change in the driving task as opposed to real-world settings in which the driver has to control the brake, gas pedal, and steering wheel at the same time. Lastly, our image discrimination task was not a natural secondary task (although one could argue that many real-world tasks such as identifying images on traffic signs or billboards or determining if an item by the roadside is a human or an inanimate object involve similar mechanisms as our image discrimination task). These factors limit the generalizability of our task to a real-world driving scenario. Future studies with even more realistic driving simulators could determine if our results can be translated to real-world driving.

Another factor worth considering in future studies is the gaze behavior of participants during dual-task interference. In our experiment, we asked participants to fixate on a fixation point at the center of the screen close to the focus of the radial optical flow pattern, which is the natural position of the gaze during driving (Lappe et al., 2000). As such it is likely that our participants have kept their eyes on the fixation point. However, since we did not have eye tracking in our experiment, we cannot be certain about the gaze behavior of our participants. Future studies could shed light on the gaze behavior and its potential effects on dual-task interference in a driving task.

To sum up, here, for the first time, we used a simulated driving environment and a DDM to explore the processing of two tasks in a naturalistic dual-task setting. Our finding revealed that performing a secondary task while driving deteriorates the driving performance, whether presented before or after the driving task. Further investigations showed this effect might be caused by slower parallel processing of the driving task in the presence of a secondary task with some delays in the process, suggesting that a hybrid model best accounts for the results. Our results could be applicable for optimizing the design of driving assistance systems such as road signs, alarm systems, and other driver interfaces to reduce accidents. They could also inform precautionary measures aimed at reducing accidents in clinical populations with impaired executive control and should be considered in future neuroscience studies aiming to explore the neural underpinnings of dual-task interference in natural settings.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Iran University of Medical Sciences (ethics code: IR.IUMS.REC.1396.0435). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MAZ: Conceptualization, methodology, investigation, formal analysis, and writing of the original draft. GHZ: Supervision and writing - review and editing. MVP: Supervision, conceptualization, methodology, and writing - review and editing. 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/fpsyg.2020.579876/full#supplementary-material

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The Relationship Among Trait Mindfulness, Attention, and Working Memory in Junior School Students Under Different Stressful Situations

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Attention and working memory are important cognitive functions that affect junior school students' learning ability and academic performance. This study aimed to explore the relationships among trait mindfulness, attention, and working memory and to explore differences in performance between a high trait mindfulness group and a low one in attention and working memory under different stressful situations. In study 1, 216 junior school students completed the Five Facet Mindfulness Questionnaire (FFMQ), and their attention and working memory were tested in a non-pressure situation. The results showed that attention had a partial mediating effect between mindfulness and working memory. In study 2, the high trait mindfulness group and the low one were tested for attention and working memory under situations with single and multiple pressures. One notable result was that the attention and working memory performances of the high mindfulness group were all significantly higher than those of the low mindfulness group in every stress situation (no stress, single stress, and multiple stresses). Other important results were that trait mindfulness moderates the relationship between stress and attention and between stress and working memory. These results suggest that trait mindfulness has a protective effect in the process by which various stresses affect attention and working memory. These findings indicate that trait mindfulness is an important psychological quality that affects the attention and working memory of junior school students, and it is also an important psychological resource for effectively coping with the impact of stress on attention and working memory. Therefore, it is possible that improving trait mindfulness may help to improve junior school students' attention and working memory and enable them to cope better with stress, thereby helping to improve academic performance. This research is of great significance for understanding the association between key psychological qualities and cognitive functions in different stressful situations. These findings also provide insight for future studies in educational psychology.

Keywords: stress, trait mindfulness, attention, working memory, junior school student

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INTRODUCTION

Attention and working memory are two important and closely related cognitive functions. Attention refers to the ability to focus one's psychological activities on something. Working memory is a system that temporarily stores and processes current information with limited capacity. As a cognitive resource, attention helps to deal with various tasks in the working memory system (Soto et al., 2005; Kumar et al., 2009; Dunning and Holmes, 2014). Previous studies have shown that both attention and working memory are closely related to students' learning ability and performance (Durbrow et al., 2000; Ayres and Sweller, 2014). Issues surrounding students' attention and working memory are currently attracting more and more attention as topics of research (Rebok et al., 2014; Rode et al., 2017; Wimmer et al., 2020). The question of which psychological or external factors affect attention and working memory has also become a topic of discussion.

In recent years, mindfulness has attracted more and more attention in psychological research (Davidson, 2010; Brown et al., 2015; Lindsay and Creswell, 2017). Mindfulness can be viewed as both a state and as a special characteristic. State mindfulness describes the non-judgmental, present-focused awareness experienced in any given moment (Medvedev et al., 2017). Trait mindfulness or dispositional mindfulness involves stable individual differences in average frequency and intensity of mindful states over time (Brown and Ryan, 2013; Jamieson and Tuckey, 2017; Mesmer-Magnus et al., 2017). It has been shown that trait mindfulness can be improved by practice, which includes mindfulness meditation as well as some mindfulness-based interventions (Cavanagh et al., 2014; Kiken et al., 2015; Quaglia et al., 2016). Mindfulness practice also has positive effects on attention and working memory. Some studies have found that mindfulness training can improve children's sustained attention (Tarrasch, 2018), protect working memory capacity (Bailey et al., 2020), and significantly improve working memory performance (Chambers et al., 2008). It can thus be inferred that high trait mindfulness may also have positive impacts on attention and working memory.

People face pressures from different aspects of modern society. According to the Yerkes–Dodson law, moderate pressure will make individuals concentrate more energy to achieve better learning and to work efficiently (Yerkes and Dodson, 1908). However, when an individual is faced with stressful situations beyond their psychological capacity, it is difficult to make effective adjustment, resulting in negative emotions such as anxiety and depression. These in turn have adverse effects on cognitive functions such as attention and hinder the completion of tasks (Myhr et al., 2019). Working memory, as a cognitive resource with limited capacity, is more vulnerable to such effects (Matthews and Campbell, 2010; Lukasik et al., 2019).

In recent years, some studies have found that trait mindfulness is a positive psychological trait that can reduce stress sensitivity (Allen et al., 2015; Lomas et al., 2017) and the impairment of cognitive function by stress. Mindfulness meditation and high levels of mindfulness can significantly reduce the damage done to the memory of college students under stressful situations and can enable the subjects to complete the corresponding tasks more stably (Limaree, 2007). Another study was conducted on soldiers who were going to be sent to the battlefield in Iraq. The results showed that among these soldiers facing great pressure, those without psychological intervention showed a decrease in working memory capacity as the departure time approached. However, among the soldiers who received an 8-week mindfulness training, the working memory capacity of those who spent more time in self-training after class did not decrease significantly. This suggests that a certain intensity of mindfulness practice can to an extent protect working memory in the face of high-stress situations (Jha et al., 2010, 2015).

In China, junior school students are generally faced with heavy academic tasks and the pressure of gaining entry to high school. What are the effects of different stress levels on the attention and working memory of junior school students? Does trait mindfulness, as a positive psychological factor, regulate the effect of stress on junior school students' attention and working memory? These problems are of great practical significance for junior school students and other groups facing high pressure. However, so far, studies on the moderating effect of trait mindfulness on attention and working memory in stressful situations and the relationships among trait mindfulness, attention, and working memory have still been extremely rare, especially in the context of junior school students, for which no relevant research reports have been found. Therefore, this research was divided into two parts to explore these issues. In study 1, the relationship among trait mindfulness, attention, and the working memory of junior school students and the internal mechanism of that relationship were explored. In study 2, stressful situations were created in an attempt to explore whether trait mindfulness has consistently positive effects on attention and working memory across a range of stressful situations, and in particular, whether trait mindfulness has moderating effects on attention and working memory in stressful situations.

The following three hypotheses were thus proposed:

H1: Trait mindfulness can predict working memory through the mediating effect of attention.

H2: In a given stress situation (no stress, single stress, or multiple stresses), there is a significant difference in the junior school students' attention and working memory performance between the high trait mindfulness group and the low one.

H3: Trait mindfulness has a moderating effect on the influence of different intensities of stress on attention and working memory.

This research enriched the theoretical research on the influencing factors of attention and working memory. From the perspective of key psychological traits, it provides important clues toward, and a scientific basis for, improving the level of attention and working memory of individuals in stressful situations and thereby improving academic performance, and it has practical significance for carrying out effective education in schools.

STUDY 1

This research was approved by the Harbin Engineering University Ethics Committee. All subjects were informed before the test of the purpose and method of the research and their right to participate. It was explained that participation was voluntary and anonymous and that there would be no penalty for withdrawing from the study at any stage without notice. The written informed consent of the subjects was obtained for all studies.

In study 1, a cross-sectional study was conducted to investigate the correlation among mindfulness, attention, and working memory in junior school students and to explore the mediating role of attention in the influence of mindfulness on working memory.

Methods

Participants and Procedures

Two hundred and seventeen junior school students who voluntarily participated in the study were studied by the convenience sampling method, and 216 valid data were finally obtained. The age range of the subjects was 9–15 years old (M = 11.88, SD = 1.20). The distribution of gender and grades was as follows: 131 boys (60.65%), 85 girls (39.35%); 106 in grade 1 (49.07%), 71 in grade 2 (32.87%), and 39 in grade 3 (18.06%). All subjects had normal intelligence and normal or corrected vision.

All studies were conducted in a quiet environment without interference or stress. The examiner used uniform instructional language to explain the purpose and specific requirements of the test. After ensuring that the subject understood the instructions, they were tested in groups for the mindfulness trait. Then individual tests of attention were performed, and 3 days later, individual tests of working memory were performed to avoid fatigue effects.

Measures

Trait mindfulness test

The Five Facet Mindfulness Questionnaire (FFMQ) is an established questionnaire that is used to assess trait mindfulness (Baer et al., 2006). In the current study, the Chinese version of the FFMQ, as revised by Deng et al. (2011), was used. It consists of 39 items rated on a five-point Likert scale from 1 = *never or very rarely true* to 5 = *very often or always true*. The FFMQ is composed of five subscales, including "observe," "describe," "actaware," "non-judge," and "non-react." Item scores are summed to form a mindfulness score, with higher scores indicating higher levels of trait mindfulness. In this study, the Cronbach's alpha value for this scale was 0.744.

Attention test

A traditional cancelation test is often used to test for attention ability (Schweizer et al., 2005). In this study, a paper-and-pen, designated digital cancelation test (**Figure 1**) was used to test the directivity and concentration of attention. The study material consisted of 1,000 Arabic digits (zero to nine). Subjects were asked to cross out the designated number 6 as quickly and accurately as possible. The ratio of the number of instances of the digit to be crossed out to the number of non-delimited digits was 1:4. The sorting distribution was uniform but not regular. The cancelation time (T) was recorded, and the cancelation accuracy was calculated as $A = (c - w) / (c + o)$, where c represents the number of digits which were crossed out, o represents the number of digits which were missed, and w represents the number of digits which were crossed out incorrectly. The attention concentration index ($E = e \times A/T$, where e represents the number of digits actually checked) was used as the final score indicator to measure attention. In this study, all the subjects completed the examination of 1,000 numbers, and thus, $e = 1{,}000$.

4	8	6	1	5	6	4	6	6	8	5	3	5	6	4	8	1	5	6	5	5	6	7	6	5
7	8	1	8	5	7	6	5	2	6	7	5	3	1	6	2	5	7	8	6	2	5	7	6	3
5	6	8	2	3	5	6	7	6	2	5	4	5	3	6	5	3	4	6	6	7	9	7	5	6
6	8	5	2	1	6	7	5	2	6	7	5	4	9	5	6	5	7	9	4	6	5	8	7	6
4	6	9	5	7	6	5	1	6	5	7	4	2	4	5	8	6	7	5	6	5	9	7	6	2
5	6	4	5	5	1	6	5	8	4	6	0	5	5	4	6	4	0	7	6	8	4	6	8	7

FIGURE 1 | Schematic diagram of the digital cancelation test.

Working memory test

The level of visual working memory was evaluated by a classical, visual graphic working memory paradigm (**Figure 2**). The test task followed the definition of working memory given by Baddeley et al. (1996), that is, information needs to be processed and stored at the same time. The test was carried out on a computer with a screen size of 33.6 cm × 27 cm and a resolution of 1,280 × 1,024. The method was to present six groups of geometric graphics successively. From the first group to the sixth group, the number of target graphics gradually increased from one to six, and the graphics gradually changed from simple to complex. Each of the graphics was presented for 4 s, and the subjects were asked to observe and remember them quickly. When a "+" appeared on the screen, it meant that the presentation of the group of graphics was completed, and there would be a pause for 4 s. Next, the subjects were asked to judge whether the direction, shape, and size of each figure in the subsequent figure group were exactly the same as in the target figure just presented. Each correct answer counted for one point, and the total score was used as the visual working memory score.

Statistical Analysis

Descriptive statistical analysis was conducted on the mean value and standard deviation of attention, working memory, and the total score and facet scores of trait mindfulness for all subjects, and Pearson correlation coefficients were calculated to analyze the correlation between variables. In addition, based on controlling the influence of age on attention and working memory, the mediating effect model of attention on mindfulness and working memory was established by using the path analysis method. Descriptive statistics and correlation analysis were performed using SPSS 22.0 (IBM Corp., Armonk, NY, United States). AMOS 21.0 (IBM Corp., Armonk, NY, United States) was used for mediating effect analysis. Significance was established at $p < 0.05$.

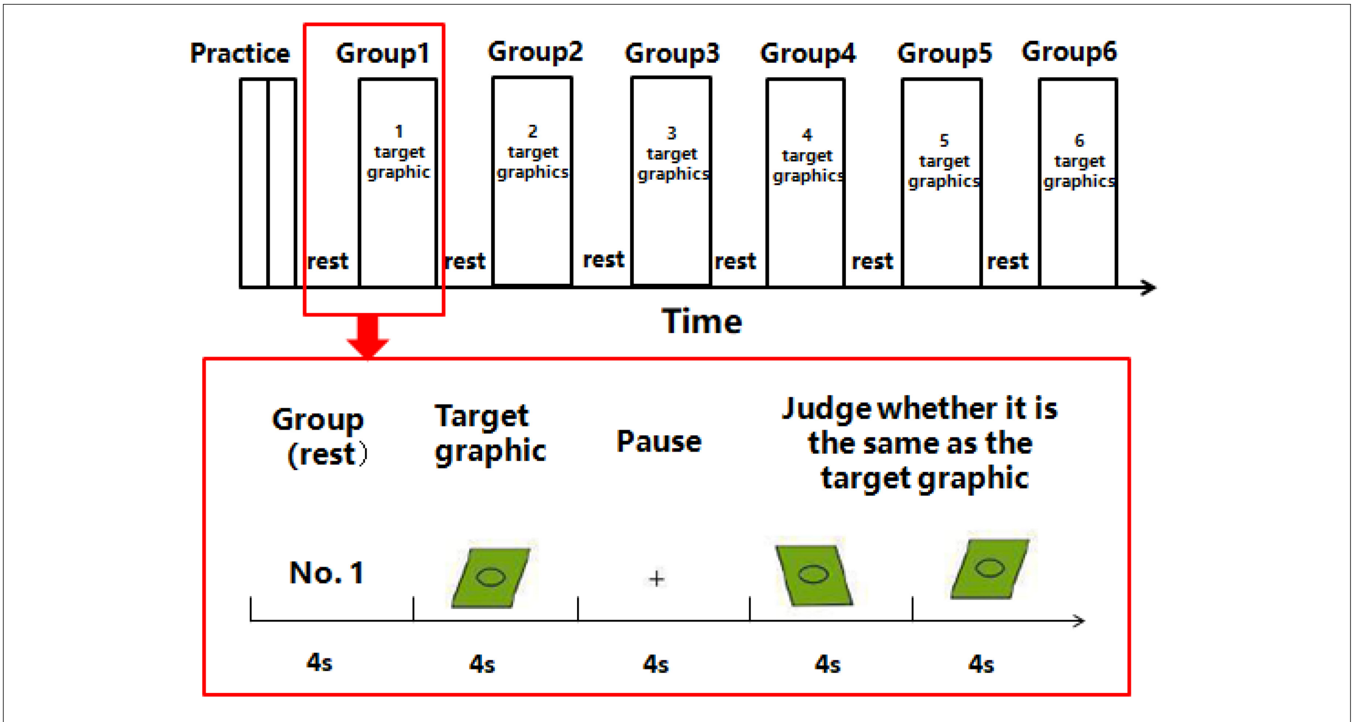

FIGURE 2 | Schematic diagram of working memory test method (take the first group of tests as an example).

Results

Descriptive Statistics and Correlation Analysis of Each Variable

The average value, standard deviation, and correlation coefficient of trait mindfulness (including total score and five facet score), attention, and working memory are shown in **Table 1**. There was a significant positive correlation between total mindfulness score, attention, and working memory. The two mindfulness facets of "observe" and "actaware" were positively correlated with attention performance, and the three mindfulness facets of "observe," "describe," and "actaware" were positively correlated with work memory performance.

Analysis of the Mediating Effect of Attention

Path analysis was used to explore the mediating effect of attention on the relationship between mindfulness and working memory, by controlling the effect of age on attention and working memory. Because the "non-judge" and "non-react" facets had no significant correlation with attention and working memory, only the sum of the other three mindfulness facets was taken as a mindfulness score when constructing the mediating effect model.

The results of the mediating effect model are shown in **Figure 3**. As the influence of age on attention and working memory was not significant ($p < 0.05$), the age is not indicated in **Figure 3**. The fitting index of this model was as follows: $\chi^2/df = 2.976$, GFI = 0.993, AGFI = 0.932, IFI = 0.990, TLI = 0.939, NFI = 0.985, CFI = 0.990. Therefore, the goodness of fit of this model was good. The non-parametric percentile bootstrap method of deviation correction was used to test the intermediate effect and estimate the confidence interval. The number of bootstrap repeated samplings was set to 5,000 and the confidence interval was set to 95%. The results showed that the confidence intervals of the mediating effects of this model do not contain zero, and the mediating effects were statistically significant (**Table 2**).

Table 2 shows the action path, effect value, and proportion of all independent variables to dependent variables in this model. Among these, the effect value for the direct effect of mindfulness on working memory was 0.40, accounting for 68.40% of the total effect. The mediating effect of attention between mindfulness and working memory was 0.18, accounting for 31.60% of the total effect.

STUDY 2

In this study, different stress situations were established to explore the effect of the interaction between stress and mindfulness on attention and working memory as well as further simple effects. A 2 (mindfulness level: low, high) × 3 (stress situation: none, single stress, multiple stresses) mixed experimental design was used. Among these, the level of mindfulness was the intersubject variable, and the stress situation was the intrasubject variable.

Methods

Participants and Procedures

According to the total score of the FFMQ scale in study 1, participants were divided into high and low mindfulness groups. Among the test subjects, the highest scoring 27% was in the

TABLE 1 | Descriptive statistics and correlation analysis of mindfulness level, attention, and working memory of junior school students (*r*).

	M	SD	1	2	3	4	5	6	7	8
1. Observe	24.22	6.22	1							
2. Describe	22.20	4.36	0.15*	1						
3. Actaware	27.00	6.09	0.15*	0.23**	1					
4. Non-judge	22.57	4.82	0.37***	0.14*	0.10	1				
5. Non-react	19.52	4.04	0.47***	0.04	0.06	0.37***	1			
6. Total score of mindfulness	115.52	14.97	0.76***	0.50***	0.49***	0.57***	0.57***	1		
7. Attention	3.34	1.07	0.42***	0.10	0.52***	0.08	0.11	0.48***	1	
8. Working memory	36.64	11.86	0.41***	0.21**	0.51***	0.05	0.08	0.48***	0.55***	1

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

high mindfulness group, and the lowest scoring 27% was in the low mindfulness group. One hundred and sixteen junior school students participated in all the tests of study 2.

The test situation of study 1 was regarded as the stress-free situation, and the test results of study 1 were thus used as the attention and working memory performance scores of the subjects in the stress-free situation. Furthermore, each subject's attention and working memory under single and multiple stresses were measured individually. All tests were conducted in a quiet environment. The examiner uniformly adopted the new instructional language to explain the purpose and specific requirements of the test. After ensuring that the subjects understood, the attention test was performed first and then the working memory test. To avoid the fatigue effect, subjects were given a 3-day interval between the attention test and the working memory test in the same stressful environment. In order to avoid the memory effect, for the same kind of test across different stress situations, subjects took parallel-form tests. In order to avoid the practice effect, the interval between the two similar tests was about 1 month.

Measures

Single stress situation

Time pressure was applied to the subjects in the single stress situation, in order to make individuals feel that it was challenging to complete the experimental task within a short time. The attention test required the subjects to complete the test within 1 min, and each picture in the working memory test was only presented for 2 s. When the examiner explained the instructions, they emphasized that the time constraints of the tests were significantly shorter than that of study 1, thereby giving the participants a sense of stress.

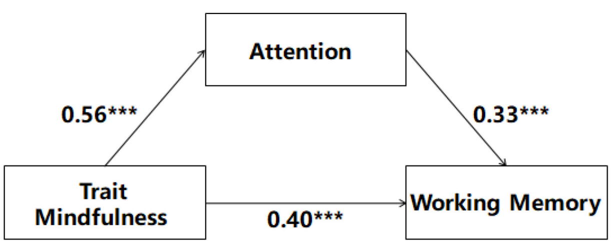

FIGURE 3 | The relationship model of trait mindfulness, attention, and working memory. ***$p < 0.001$.

A copy of the number cancelation test was used as the experimental material to test attention in this situation. Compared with study 1, the completion time for the single stress situation was shortened to 1 min, the designated erasure number was adjusted from six to five, and all the number sorting was readjusted; other settings were unchanged.

A copy of the visual graphic working memory test was used as the experimental material to test working memory in this situation. Compared with study 1, the rendering time of the replica was shortened to 2 s, and the size, direction, or order of the target and alternative graphics were adjusted; other settings were unchanged.

Multiple stress situation

The premise of the multiple stress situation was to add situational pressure on top of time pressure, so that the subjects would feel the combined effect of more types of pressure. The time pressure was established in the same manner as described above. In China, learning ability and whether they are valued by teachers are important factors that affect the self-evaluation of junior school students. Therefore, when the examiner explained the instructions, it was emphasized that the participant's teacher would be informed of the results of the attention and working memory test as an indicator to evaluate their learning ability, and the teacher would focus on training the top students in the follow-up teaching. At the end of all the experiments, the students were informed of the real situation, i.e., the test results were actually confidential and would not be disclosed to the teachers, nor would they influence the teachers' evaluation and subsequent training of the students, so as to avoid any negative impact of the test on the students' psychological state.

The interval between this test and the single stress situation test was 1 month, while the interval between this test and the study 1 test was 2 months. In order to avoid a memory effect of the test materials in the single stress situation, the attention and working memory experimental materials from study 1 were reused, but the time setting was the same as that in the single stress situation.

Statistical Analysis

Descriptive analysis of attention and working memory scores under different stress situations and at different

TABLE 2 | Action path, effect size, and proportion of each variable in the model to working memory.

Path	Standardized effect value	Effect ratio	95% CI
Direct effect: mindfulness → working memory	0.40	68.40%	[0.28, 0.52]
Indirect: mindfulness → attention → working memory	0.56 × 0.33 = 0.18	31.60%	[0.12, 0.26]
Total effect	0.58		[0.49, 0.66]

TABLE 3 | Attention scores under different stress situations and mindfulness levels (*M* ± SD).

		Stress situation		
		Stress-free situation	Single stress situation	Multiple stress situation
Mindfulness level	High mindfulness group (*n* = 58)	4.04 ± 1.22	5.64 ± 1.39	4.69 ± 1.15
	Low mindfulness group (*n* = 58)	2.68 ± 0.69	1.29 ± 0.78	1.20 ± 0.76

levels of mindfulness was performed, with data expressed as mean ± standard deviation. The 2 × 3 mixed variance analysis was used to analyze the interaction effect and simple effect of the data. The independent variables were trait mindfulness and stress situation, and the outcome variables were attention and working memory. SPSS 22.0 (IBM Corp., Armonk, NY, United States) was used for analysis. The significance threshold was set at the $p < 0.05$ level.

Results

The Influence of Stress Situation and Mindfulness Level on Achievement at the Attention Task

The attention scores for different stress situations and mindfulness levels are shown in **Table 3**. The results of ANOVA showed that the interaction between mindfulness level and stress situation was significant [$F(2,114) = 207.94$, $p < 0.001$, $\eta^2{}_p = 0.646$]. These results are presented in **Figure 4**. Further simple effect analysis showed that (1) there was a significant difference in the attention performance of the high mindfulness group under different stress situations [$F(2,56) = 81.81$, $p < 0.001$]. Further results showed that the attention performance of the high mindfulness group was significantly better in the single stress situation than in the multiple stress situation, and the attention performance in the multiple stress situation was also significantly higher than that in the stress-free situation. The attention level of the low mindfulness group decreased with the increase in stress, but the difference was not significant [$F(2,56) = 26.51$, $p > 0.05$]. (2) The attention scores of the high mindfulness group and the low one were significantly different in each stress situation. In a stress-free situation, $F(2,56) = 54.61$, $p < 0.001$. In the single stress situation, $F(2,56) = 434.05$, $p < 0.001$. Under the multiple stress situation, $F(2,56) = 373.06$, $p < 0.001$. These results show that in all three different stress situations, the attention performance of the high mindfulness group was significantly higher than that of the low mindfulness group.

FIGURE 4 | Interaction between stress situations and mindfulness levels on attention scores. 1 is stress-free situation, 2 is single stress situation, and 3 is a multiple stress situation.

Effect of Stress Situation and Mindfulness Level on Working Memory Performance

The results of working memory under different stress situations and different mindfulness levels are shown in **Table 4**. The results of ANOVA showed that the interaction between mindfulness level and stress situation is significant (**Figure 5**), and $F(2,114) = 72.31$, $p < 0.001$, $\eta^2{}_p = 0.388$. Further simple effect analysis showed that the working memory performance of the low mindfulness group was significantly different under different stress situations [$F(2,56) = 258.28$, $p < 0.001$]. Further results showed that the working memory performance of the low mindfulness group in the stress-free situation was significantly better than that in the single stress situation, and their working memory performance in the single stress situation was significantly higher than that in the multiple stress situation. There was no significant difference in the working memory scores of the high mindfulness group under different stress situations [$F(2,56) = 2.21$, $p > 0.05$]. The difference in working memory performance between the high mindfulness group and the low one in each stress situation was significant. In the stress-free situation, $F(2,56) = 247.1$, $p < 0.001$. In the single stress situation, $F(2,56) = 247.1$, $p < 0.001$. Under the multiple stress situation, $F(2,56) = 550.21$, $p < 0.001$. This shows that the working memory performance of the high mindfulness group was significantly higher than that of the low mindfulness group in all three different stress situations.

TABLE 4 | Working memory performance under different stress situations and mindfulness levels ($M \pm$ SD).

		Stress situation		
		Stress-free situation	**Single stress situation**	**Multiple stress situation**
Mindfulness level	High mindfulness group (n = 58)	43.59 ± 1.47	41.16 ± 0.75	42.64 ± 1.01
	Low mindfulness group (n = 58)	30.00 ± 1.05	20.90 ± 1.05	12.33 ± 0.81

DISCUSSION

The results of study 1 showed that there were positive correlations among trait mindfulness, attention, and working memory and that attention had a partial mediating effect between trait mindfulness and working memory, verifying Hypothesis 1. It can be seen that, on the one hand, the higher the level of trait mindfulness, the more concentrated and stable the individual's attention can be when completing the task, thus better promoting working memory. On the other hand, trait mindfulness can also directly affect working memory levels.

The close relationship between trait mindfulness and attention was consistent with the results from prior studies. It has been found that the human mind wanders for nearly half of its waking time (Killingsworth and Gilbert, 2010), and trait mindfulness and mindfulness training are associated with reduced mind wandering (Mrazek et al., 2012, 2013). Mindfulness controls attention by reducing habitual distribution of attention and attention to distracting information (Wadlinger and Isaacowitz, 2011). It is worth noting that the two mindfulness facets of "observe" and "actaware" were positively correlated with performance on the attention test in study 1, suggesting that these two facets may be the important factors of trait mindfulness affecting attention. The higher the level of trait mindfulness, the more consciously the individual can observe and pay attention to all kinds of experiences, pay more attention to and be aware of their current actions, and then have better performance when completing the attention task test.

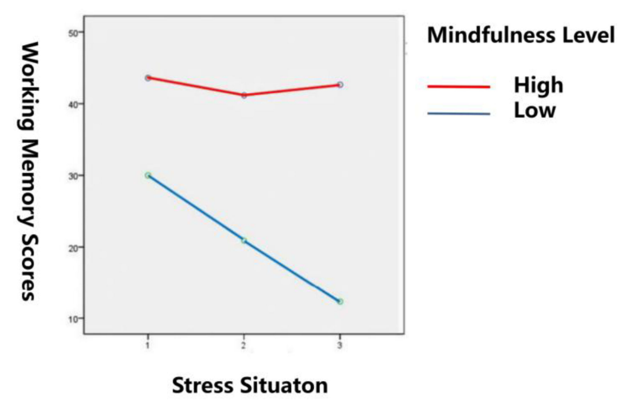

FIGURE 5 | Interaction between stress situations and mindfulness levels on working memory scores.

In this study, trait mindfulness was found to be related to working memory and positively influenced working memory performance. This is consistent with the results of previous studies (Phillipot and Segal, 2009; Satish et al., 2018). In the process of the influence of trait mindfulness on working memory, 31.60% were realized through the mediation of attention. This is because attention plays a fundamental role in cognitive processes, and this is very important in working memory. It is the first step of information processing by which external information enters the current processing range through attentional selection. On this basis, the further processing of information can be completed by working memory (Cowan et al., 2006). The results of this study also showed that the two mindfulness facets of "observe" and "actaware" are positively correlated with working memory. As mentioned before, these two facets are also positively correlated with attention. In conclusion, these two mindfulness facets can influence working memory through the mediation of attention.

Our results showed that the direct effect of trait mindfulness on working memory was 0.40, accounting for 68.40% of the total effect. This result indicates that apart from attention, trait mindfulness may directly or indirectly affect working memory through other mediating factors and that these effects were greater than those of attention. However, so far, the direct psychological mechanism of mindfulness affecting working memory is still unclear. This study showed that the "describe" facet of trait mindfulness is positively correlated with working memory, but not with attention, suggesting that the "describe" facet may be one of the internal mechanisms by which trait mindfulness directly affects working memory. The higher the "describe" facet score, the more likely the individual is to describe and mark internal experiences with language in daily life (Baer et al., 2006). When taking part in the working memory test, such individuals tend to use internal language to describe and mark the figures in the task. This internal processing strategy helps to make memory clearer and stable, resulting in better working memory test scores. However, it should be noted that the correlation coefficient between the "describe" facet and working memory performance is 0.21, a low-level correlation. Therefore, the direct impact of trait mindfulness on working memory must have other psychological mechanisms, which need further study in the future.

In addition to the above, the reason that trait mindfulness can positively predict attention and working memory may also be related to brain function and brain structure. Most previous research has focused on the impact of mindfulness training on the brain, and only several limited studies evaluating the neural basis of trait mindfulness have shown that trait mindfulness may be related to brain regions involved in attention and working memory, such as the hippocampus (Taren et al., 2013), the double lateral anterior cingulate cortex (ACC) (Lu et al., 2014), etc., and that brain function, neuroelectric activity, and even the structure of these brain areas and other areas related to attention and working memory can be changed through mindfulness practice (Cahn et al., 2010; Wang and Huang, 2011). Therefore, it can be speculated that mindfulness traits may be one of the important psychological factors in understanding the effects of mindfulness exercises on attention and working memory. That is to say, the positive influence of mindfulness exercise on attention and working memory may be achieved by improving the level of trait mindfulness and inducing changes in the corresponding brain structures and functions.

The experimental results of study 2 showed that the attention and working memory scores of the high trait mindfulness group were higher than those of the low trait mindfulness group across all three stress situations (no stress, single stress, and multiple stresses), verifying Hypothesis 4. These results also further deepened the results of study 1. They showed that the positive correlation and influence of trait mindfulness on attention and working memory were consistent across contexts; i.e., whether the stress intensity was great or not, the performance of attention and working memory from those with high trait mindfulness was always better than that from those with low trait mindfulness. These results showed that the level of trait mindfulness can be used to predict the performance of attention and working memory in different stress situations.

In study 2, we also found that stress situations and trait mindfulness interact in the process of influencing attention and working memory. Further simple effect analysis showed that the effects of different stress situations on attention and working memory are regulated by trait mindfulness, verifying Hypothesis 5. To be specific, based on the attention test scores under different stress situations, the relative performance of the high trait mindfulness group on the attention test were as follows: single stress > multiple stresses > no stress. However, for the low trait mindfulness group, although no statistical difference was found in attention under the different stress conditions, it can be seen in **Table 3** and **Figure 4** that attention had a downward trend in the process from no stress to single stress and multiple stresses. There was no significant change in the test results for working memory across the different stress situations for the high mindfulness group. The working memory performance of the low mindfulness group decreased significantly with the increase of stress intensity.

According to the Yerkes–Dodson law, stress and task performance show an inverted U-shaped curve. When the pressure is moderate, the task performance is the highest. Excessive stress will lead to a decline in task performance. However, whether a stress situation constitutes excessive pressure and how much influence it will have are affected by many factors. According to the interaction theory of stress coping, the influence of stress on individuals is related not only to changes in the stimulating environment or events but also to psychological factors such as individual cognition and coping style (Lazarus and Folkman, 1984). The results of this study showed that trait mindfulness is an important psychological factor that regulates the influence of stress on individual attention and working memory.

For the low trait mindfulness group, working memory decreased significantly with the increase in stress intensity. Although the performance of attention did not show a significant difference, there was a downward trend. This shows that for such individuals, the single stress and multiple stress levels established in this experiment exceed the highest stress level that the participants could bear, resulting in a decline of working memory and attention. Therefore, it is suggested that for such individuals, the degree of stress tolerance is very limited, and a small increase in stress may have a strong negative impact on them. Therefore, in normal learning tasks, time pressure and other factors that could readily cause stress should be reduced, to avoid damaging working memory and attention.

It has been found that increased trait mindfulness can reduce stress sensitivity (Greeson and Gabrielle, 2018). Individuals with high trait mindfulness have less stress sensitivity and better adaptability than those with low trait mindfulness (Grover et al., 2016; Lomas et al., 2017). For high trait mindfulness individuals, the single time stress situation used in this study is close to the appropriate range of stress (the highest point of the inverted U curve). This may enable individuals to reach or approach the best level of arousal, stimulate individual potential, and fully mobilize attention. This helps the individual to complete the attention test quickly and accurately and to make the score on the attention test reach or approach the best possible level. Under the multiple stress condition, the stress intensity exceeds the individual's ability to bear properly, and so, test scores decline. However, when the individual is in a stress-free situation, the potential of the individual, including attention and other cognitive resources, is not effectively mobilized, yielding the lowest score for all three conditions. Therefore, for the high trait mindfulness group, in the normal learning tasks, increasing the stress intensity appropriately, such as increasing the time pressure properly, will be more conducive to the individual's concentration and to faster and better completion of the task. In the working memory test, with the increase in stress intensity, the performance of working memory in the high trait mindfulness group was not damaged, indicating that high trait mindfulness had a protective effect on the working memory of individuals coping with stress.

This study yielded another interesting and noteworthy result. Regardless of whether the participant was in the low trait mindfulness group or the high trait mindfulness group, as the stress situation changed, the changes in individual working memory were not synchronized with changes in attention. For example, in the low trait mindfulness group, as the stress increased, working memory decreased significantly, but the performance of attention did not change significantly. In the high trait mindfulness group, the relative scores on the attention test, across all three stress conditions, were as follows: single stress > multiple stresses > no stress, but there were no significant differences in scores for working memory. This may be due to the fact that, although attention is an important factor affecting working memory (Oberauer, 2019), working memory may also be affected by other factors such as emotions

(Eysenck et al., 2005) and expectation-driven changes in cortical functional connectivity (Bollinger et al., 2010). Moreover, these factors may have different effects on working memory in different stressful situations, which may lead to the observed asynchrony of the attention and working memory test results.

In conclusion, this study suggests that a good way to improve attention and working memory in different stress situations would be to improve the level of trait mindfulness. Therefore, this study provides a strong theoretical basis and practical guidance for improving attention and working memory.

Limitations and Future Research

Although this study produced some important findings, it nonetheless has some limitations. First, with regard to research methods, study 1 adopted a cross-sectional design, and thus, it could not draw any conclusions regarding causality; this should be borne in mind when interpreting the results from study 1. Second, with regard to the research group, the subjects selected in this study were all junior school students, from a single sample source. The research conclusions may not be applicable to other groups, raising potential concerns about external validity. Third, with regard to the research content, although this study discussed the possible role of the brain in the process by which trait mindfulness affects attention and working memory, that was only a deduction and no substantive research on that specific topic was conducted.

Therefore, the following aspects need to be further explored in the future. First, a longitudinal study or combined mindfulness interventions should be considered to explore the dynamic relationship among trait mindfulness, attention, and working memory, so as to further verify the causal relationship among them. Second, attention and working memory are very important not only for junior school students but also for other groups. Therefore, one could further expand the scope of the subjects and thereby yield meaningful knowledge for promoting the attention and working memory performance of other groups. Finally, studies on the relationship between brain function and structure and trait mindfulness are still rare, and this aspect should be studied to further clarify the effective mechanisms by which trait mindfulness affects attention and working memory.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of confidentiality and ethical restrictions. Requests to access the datasets should be directed to the corresponding author.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

YL was responsible for writing the manuscript and analyzing the data. NY was responsible for designing the research and collecting the data. YZ conducted the experiment and reviewed and revised the manuscript. WX took part in designing the research and collecting the data. LC took part in collecting the data. All authors approved the above version to be published.

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The Effect of Spatial Ability in Learning From Static and Dynamic Visualizations: A Moderation Analysis in 6-Year-Old Children

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Previous studies with adult human participants revealed mixed effects regarding the relation between spatial ability and visual instructions. In this study, we investigated this question in primary young children, and particularly we explored how young children with varying levels of spatial abilities integrate information from both static and dynamic visualizations. Children (*M* = 6.5 years) were instructed to rate their invested mental effort and reproduce the motor actions presented from static and dynamic 3D visualizations. The results indicated an interaction of spatial ability and type of visualization: high spatial ability children benefited particularly from the animation, while low spatial ability learners did not, confirming therefore the ability-as-enhancer hypothesis. The study suggests that an understanding of children spatial ability is essential to enhance learning from external visualizations.

Keywords: multimedia learning, spatial ability, young children, animation, cognitive abilities

INTRODUCTION

Issues of spatial ability and learning achievement have been an underlying topic of psychological and educational discussions for many years (e.g., Presmeg, 1986; Wanzel et al., 2002; Unal et al., 2009). Concerning the spatial ability and its influence on learning from static and dynamic visualizations, numerous research has been conducted (e.g., Höffler, 2010; Höffler and Leutner, 2011; Nguyen et al., 2012; Berney et al., 2015; Castro-Alonso et al., 2018; de Koning et al., 2019; Kühl et al., 2018; Castro-Alonso et al., 2019a; Castro-Alonso et al., 2019b). However, studies investigating the effect of visualization type and spatial ability on children learning performances are lacking. Our study is, therefore, an attempt to directly examine this issue in the context of multimedia learning. Two principal research questions oriented this investigation: First, what external visualization will lead to the best understanding of a 3D game sequence in 6-year-old children? Second, does the efficiency of an external visualization depend upon children spatial ability?

Dynamic visualizations such as animations and videos can nowadays be easily integrated into a multitude of learning and training environments (Sherer and Shea, 2011; Kay, 2012; Khacharem et al., 2015a; Berney and Bétrancourt, 2016). It has been known that dynamic visualizations may facilitate learning as the learner can explicitly (and directly) perceive spatiotemporal changes in the depicted system/procedure. In the case of static visualizations, on the other hand, the learners have to mentally imagine spatiotemporal changes, which is assumed to be more challenging. Another argument suggests that the unequivocal depiction of a dynamic event through an animation can help the learner avoid misinterpretations of motion indicators used in static pictures, such as arrow symbols. Khacharem et al. (2015b) give the example of a diagram of play in which arrow symbols are used to depict players' motion. Learners might incorrectly interpret/understand the significance and the amplitude of the depicted arrows. This may impose significant levels of cognitive load and lead to misunderstanding and consequently, to a deficient mental model (Lewalter, 2003; Khacharem et al., 2020). Additionally, the external depiction of a movement by a dynamic visualization is considered to be more entertaining and engaging than equivalent static visualizations, which may, in turn, lead to better learning results (e.g., Lepper and Malone, 1987; Rieber, 1991; Khacharem, 2017). Recently, some evidence has demonstrated that dynamic visualizations seem to be particularly efficient for teaching procedures/contents that are realistic, based on human movements, and involving procedural-motor knowledge (Höffler and Leutner, 2007).

However, it has been shown that the fleeting nature of dynamic visualizations generates transient information that can slow down their learning effectiveness (Ayres and Paas, 2007). The transient information effect is a loss of learning due to information disappearing before the learner has time to adequately process it or link it with new information (Sweller et al., 2011). Cognitive Load Theory (Sweller, 1994; Van Merrienboer and Sweller, 2005) suggests that the transitory nature of animations may impose extraneous cognitive load due to the temporal limits of working memory. When learning with dynamic visualizations, one frame is displayed at a time, and once the dynamic visualization has advanced beyond a given frame, that frame is no longer available to the learner. In this case, learners are required to process current information and integrate it with previous information at the same time. Such cognitive-perceptual processing may impose a higher cognitive load on working memory resources. Another argument suggests that animations may generate an illusion of understanding (Hegarty et al., 2003; Rebetez et al., 2010). An animation that provides the succession of steps and transformations over time from beginning to end (without interactivity) does not mobilize cognitive investment, but rather promotes passive rather than active learning.

Learning from external visualizations is considered to be an active process that is influenced by the prerequisites of the learner. One crucial factor mediating the effectiveness of such processes is learner spatial ability (e.g., Hegarty and Kriz, 2008; Schnotz and Rasch, 2008). Spatial ability refers to a group of cognitive functions and aptitudes that is crucial in manipulating and processing visuospatial information (Lajoie, 2008; Castro-Alonso and Atit, 2019). Spatial visualization ability is a measure of the ability to mentally rotate or fold objects and to imagine the changes in location and form due to this manipulation (e.g., Mayer and Sims, 1994). This ability varies significantly within humans; some individuals have a facility for transforming spatial information, while others find these processes very challenging (Caroll, 1993; Hegarty and Waller, 2005). Currently, two different hypotheses are employed to explain the relation between spatial abilities and presentations formats.

The ability-as-compensator hypothesis (Mayer and Sims, 1994; Höffler, 2010; Höffler and Leutner, 2011) posits that dynamic visualizations can assist low spatial ability learners by offering an explicit representation of temporal aspects of the system, thus reducing the need to mentally animating the static information. However, high spatial ability learners do not gain particular benefit from dynamic visualization because they are more cognitively equipped to generate an adequate mental representation of the depicted content regardless of the presentation format (Mayer, 2001). For example, Höffler and Leutner (2011) investigated the respective role of spatial ability and type of visualization (animation versus a series of static pictures) on learning of chemistry concepts. Spatial ability was measured using the Paper Folding test and the Card Rotation test (Ekstrom et al., 1976). The results indicated that low-spatial ability learners showed poor learning outcome when learning from static pictures while high-spatial learners did not. Conversely, when learning from animation, spatial ability did not moderate learning outcome as low and high spatial ability learners performed equally (Lee and Shin, 2012; Berney et al., 2015; Sanchez and Wiley, 2017).

On the other hand, the enhancer hypothesis (Hegarty and Sims, 1994; Hegarty, 2005; Huk, 2006; Höffler, 2010) claims that high spatial ability learners should uniquely benefit from the dynamic visualizations as they have enough cognitive capabilities left for mental model building of the content to-be-learned (Mayer, 2001; Huk, 2006). However, spatial ability learners experience an increase of unnecessary cognitive load while learning with static visualizations because their ability to mentally animate spatio-temporal information is limited (Hegarty and Sims, 1994; Hegarty, 2005; Huk, 2006; Keller et al., 2006; Höffler, 2010). Huk (2006) found that the incorporation of dynamic 3D models depicting a plant/animal cell enhance learning outcomes only in high spatial ability learners who are cognitively better ready to process dynamic visualizations since they have enough cognitive capacity left for building a coherent representation of the content to be learned. In contrast, low spatial ability learners are cognitively loaded by dynamic visualizations; therefore, they performed better with static visualizations.

A closer look at the aforementioned studies reveals that relatively little attention has been devoted to understanding the role of spatial abilities when learning from external visualizations in young children. Terlecki and Newcombe (2005) noted that young children have greater experience with modern multimedia technologies such as videos and computerized animations and, as a result, spatial ability could play an important role in learning processes. Previous research on spatial acquisition has indicated that mental paper folding emerges at 5.5 years of age and develops through early primary school (Harris et al., 2013). Similarly, it has been shown that enhancement in the ability to perform the object-based spatial transformations that necessitate spatial manipulation of mental image occurs from 5 years-old, although at a slower speed than adults (e.g., Frick et al., 2009; Funk et al., 2005; Kosslyn et al., 1990; Marmor, 1977; Crescentini et al., 2014). The purpose of this study was to explore the relative effects of spatial ability and type of visualization on children ability to learn a 3-D game sequence. This study employed the Mental Folding Test for Children (MFTC; Harris et al., 2013) and the Children's Mental Transformation Task (CMTT; Levine et al., 1999; Ehrlich et al., 2006) in which adequate validity and reliability on assessing spatial visualization ability in children have been established. First, we hypothesized that watching an animation that explicitly depicted learning contents would result in better learning outcomes than watching a series of static pictures (Hypothesis 1). Second, based on the ability-as-compensator hypothesis, we expected that children with low spatial ability would principally benefit from animation, whereas children with high spatial would benefit equally from both static pictures and animation (Hypothesis 2).

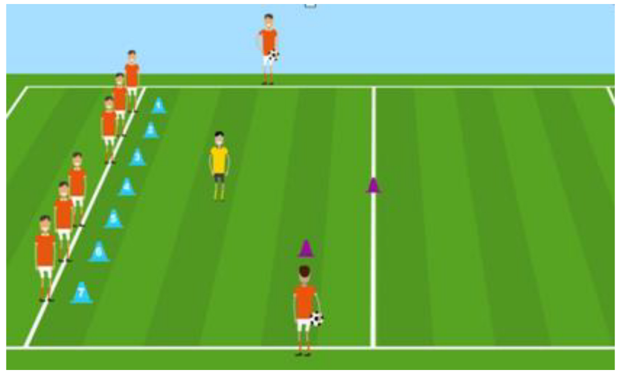

FIGURE 1 | A screenshot from the 3D game animation.

MATERIALS AND METHODS

Participants

A sample of 64 children (M = 6.5 years; SD = 0.23; 50% girls) in Grade 1 participated in this study. Children with intellectual disability, neurological disorder and/or uncorrectable hearing and/or visual impairment were excluded. They had not previously taken part in any similar research. The parents were required to consent to the inclusion of their child in the study and provide basic information on the child's developmental history. The study was conducted according to the Declaration of Helsinki and fully approved by the Sfax University Ethics Committee (approval code CPP 0076/2017)" before the commencement of the study.

Material Learning

A 3-D game sequence titled "the passing game" was designed and developed using Macromedia Flash MX Professional 2004. The game contained 10 players positioned as follows: seven players on the bottom line (attackers) and one player on each sideline (playmaker). It started with the teacher designing the number of an attacker (from 1 to 7) and ended with the designed attacker grounding the ball over the goal line. The game consisted of 11 steps. During each step, the attacker carried a set of actions: dribbling, hand passing, walking and accelerating. The game sequence of 47*sec* was presented via either an animation or a series of 12 static pictures representing the key moments of the sequence. Both versions were accompanied by the same verbal commentary. The learning and output stimuli were presented on a 17-inch LCD computer screen with a 1,280 × 1,024-pixel display. **Figure 1** gives a screenshot from the 3D game sequence used in the study.

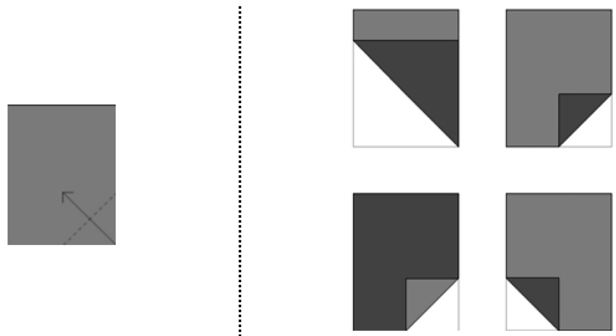

FIGURE 2 | The Mental Folding Test for Children.

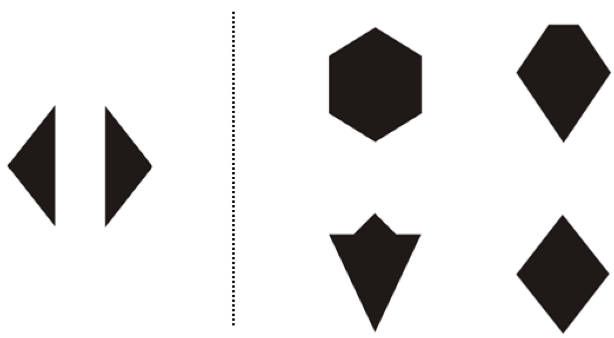

FIGURE 3 | The Children's Mental Transformation Task.

Measures

Spatial Ability

Children's individual spatial ability was evaluated by two different tests. The MFTC (Harris et al., 2013) is a test developed for measuring the 4–7 years old children's ability to fold 2D shapes in their mind. It is a multiple-choice test where both sides of the shapes are presented in different colors. **Figure 2** shows one of the test items of the MTFC.

Another measure was the CMTT (Ehrlich et al., 2006; Levine et al., 1999) which consists of a multiple-choice test asking 4–7 years old children to point out the shape that will come into being when the previously presented two shapes are combined. **Figure 3** shows one of the test items of the CMTT.

For each test the percentage of correctly solved items related to the total number of items was calculated; the mean of the two scores represented each participant's spatial abilities. **Figure 4** shows the distribution of the 6 years-children's spatial ability in

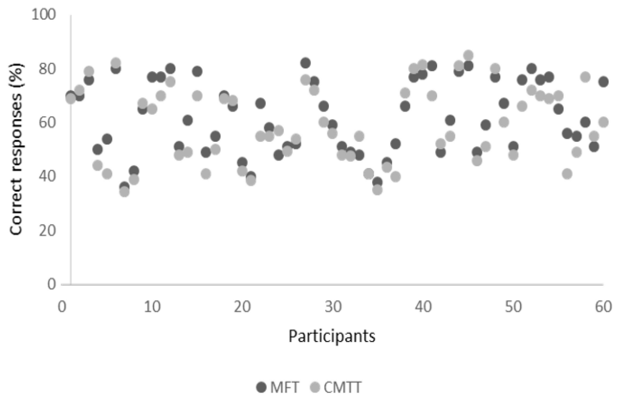

FIGURE 4 | The distribution of the 6 years-children's spatial ability in each test.

FIGURE 5 | Pictorial illustration of the mental effort scale for children (from very low mental effort – at left – to very high mental effort – at right).

each test. The correlation of MFT and CMTT was significant with $r = 0.88$.

Self-Report of Mental Effort

The experimenter explained to the children that he would like to know how they were feeling after the learning phase. In particular, they instructed them to indicate "*How much thinking did you do to complete the task; did you do a lot of thinking or only a little*?" Subsequently, the experimenter presented a picture and said: "*In this picture, the little boy seems to be thinking very hard*." Then the experimenter pointed to the other picture and said, "*In this picture, he does not seem to be thinking hard at all. How did you feel in the task you just performed*? Finally, the experimenter asked children to place a hash mark between the two pictures (100-mm) and encouraged them to use the full range of the line. Scores were determined by measuring the placement of the hash mark on the 100-mm line. The children were reassured that there were no right or wrong answers. **Figure 5** provides a pictorial illustration of the mental effort scale.

Motor Recall Performance

Children were asked to accurately recall and execute – in a well-arranged area form the schoolyard – the game sequence. To ensure a smooth running of the situation an individual was instructed to intervene – by providing an oral corrective feedback – each time the children performed a wrong action. For each correct action in the recall test, the participants were assigned one point with a maximum score of 15 points, otherwise, they received zero points.

Hesitation Time

This variable represents the time that elapses between the end and the start of a new action made by the participant. It corresponds to the moments of immobility or steps backward (recall of already executed actions).

Procedure

The session lasted about 30 min, and only one child was tested in each session. First, children completed the spatial ability tests. Afterward, each child was randomly assigned to one experimental condition and was instructed to memorize as precisely as possible the evolution of the game sequence after viewing it one time only. Finally, after the learning task, the computer was switched off, and the post-tests were administered.

Statistical Analysis

To test the mediating effect of spatial ability, we performed mediation analysis using the pre-specified Model 1 of PROCESS macro (Hayes, 2013). PROCESS application developed by Preacher and Hayes (2008) which is an SPSS procedure (PROCESS, v2.13) that facilitates path analysis and mediation analysis by using ordinary least squares regression (Hayes et al., 2017). An analysis using 5,000 bootstrap samples with 95% confidence levels of the CIs was performed after mean-centering the continuous predictor variables. Three separate moderation analyses were performed in which spatial ability served as moderator variable and recall performance, hesitation time or subjective ratings of cognitive load were used as dependent variables. Significance was accepted for all analyses at the level of $p \leq 0.05$.

RESULTS

The results for motor recall performance show a significant regression model, $R^2 = 0.57$, $p < 0.01$. The regression analysis showed significant main effects of both spatial ability [$\beta = 0.419$, se(HC4) = 0.094, $p < 0.001$] and condition [$\beta = -1.004$, se(HC4) = 0.218, $p < 0.001$] on recall, and an interaction effect between spatial ability and condition [$\beta = -0.088$, se(HC4) = 0.06, $p = 0.04$]. Children with high level of spatial ability performed significantly better in the animation condition than in the static condition, while children with low spatial ability achieved the same performance regardless the experimental condition (**Figure 6**).

The results for cognitive load showed a non-significant regression model, $R^2 = 0.078$, $p = 0.137$. The regression analysis showed no main effect for spatial ability [$\beta = 0.048$, se(HC4) = 0.159, $p > 0.05$], a marginal main effect of condition [$\beta = 0.467$, se(HC4) = 0.261, $p = 0.06$], and no interaction of spatial ability and condition [$\beta = -0.060$, se(HC4) = 0.093, $p > 0.05$].

The results for hesitation time showed a regression model, $R^2 = 0.191$, $p = 0.002$, that was significant. The regression analysis showed a significant main effect for spatial ability [$\beta = -0.507$, se(HC4) = 0.181, $p = 0.007$], no main effect of condition [$\beta = 0.703$, se(HC4) = 0.399, $p = 0.10$], and a marginally

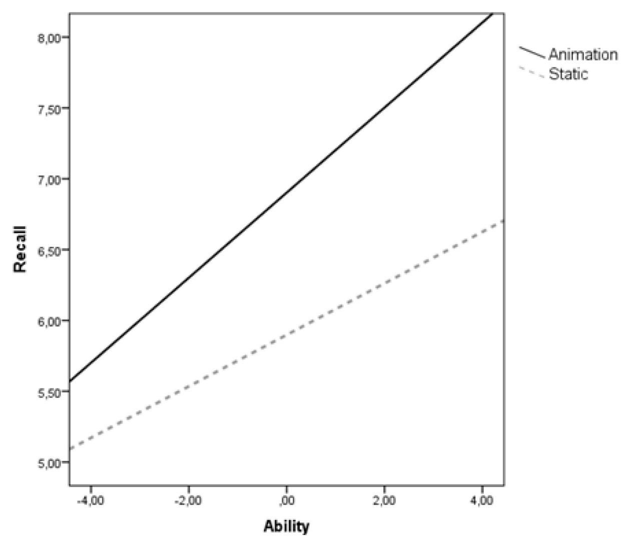

FIGURE 6 | Motor recall performance moderated by spatial ability.

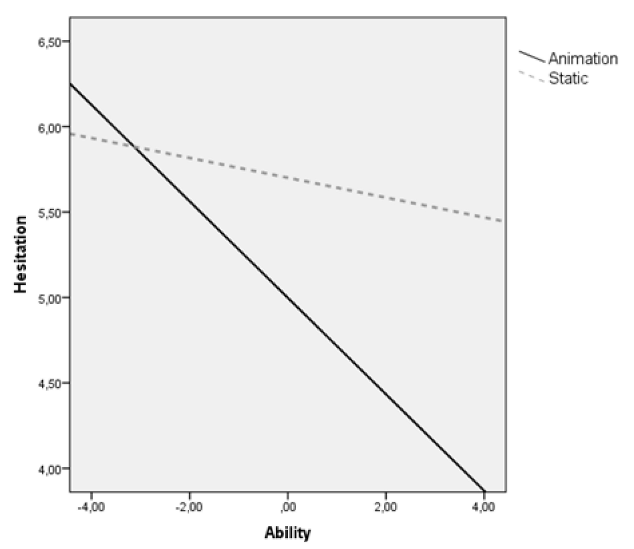

FIGURE 7 | Hesitation time moderated by spatial ability.

significant interaction effect between spatial ability and condition [$\beta = 0.224$, se(HC4) = 0.123, $p = 0.07$]. Children with high level of spatial ability reduce their hesitation time in the animation condition compared to the static condition, while children with low spatial ability keep the same hesitation time regardless the type of visualization (**Figure 7**).

DISCUSSION

In the current study, a group of primary school children were asked to remember and execute 12 elements of play, shown from static and dynamic 3D visualizations. The moderating role of spatial ability was investigated with respect to motor recall performance, hesitation time and experienced cognitive load.

In line with Hypothesis 1, the results of this study showed that children receiving animations performed better compared to children receiving the static pictures (i.e., they achieved higher motor recall, invested less mental load, and needed less time). This indicates that the explicit presentation of the dynamic aspect of the game such as trajectory and motion helped children in constructing a deeper understanding of the game sequence. Thereby, this dynamic information can directly be read off from the animation, which in turn reduces extraneous cognitive load and incertitude (expressed by the hesitation time before each motor recall). In contrast, with static pictures, this dynamic information needs to be inferred by children via an animation mental process, which is generally assumed to be a more demanding cognitive task than merely perceiving temporal changes (Hegarty et al., 2003). Moreover, previous research have revealed that dynamic visualizations can be more effective form of instruction if they are realistic and involve procedural knowledge (Höffler and Leutner, 2007; Ayres et al., 2009; Wong et al., 2009; Garland and Sanchez, 2013; Castro-Alonso et al., 2015). In this research, we used animations that followed the prescriptions of this earlier research.

Another important finding of this study was the significant interaction found between spatial ability and type of visualization indicating an ability—as—enhancer hypothesis. Children with high spatial ability performed better from animation rather than static pictures (i.e., they achieved higher motor recall, needed less hesitation time and invested the same amount of mental load). It seems that these learners had already developed cognitive capabilities that enabled them to fluently process the fleeting dynamic information without a cognitive overload. However, in the static presentation, they would need to reconcile their cognitive resources with instructional details that were for them redundant and superfluous, which might impose additional extraneous cognitive load and reduce relative general performance. On the other hand, the results revealed that children with low spatial ability do not gain particular benefit from animation (i.e., they achieved the same recall motor score, they invested same amount of mental load and needed the same hesitation time). Because animations change continuously over time, these learners may not be able to process and integrate specific key elements of information that occur within the flow of information (e.g., Lowe, 1999; Rasch and Schnotz, 2009). In contrast, learning from static pictures is self-paced in the sense that learners were allowed as much time as they needed to reinspect a particular information. Therefore, it is likely that interactive animations, which allow children to control the progress of the animation, might be more helpful than animations that play at a fixed rate.

As is the case for all experimental studies, there are some limitations to the generalizability of our results. The limiting variables include the participants used for this research, which included primary school children (in Grade 1); the subject matter area, which focused on motor-procedural learning; and the design of learning materials used, which consisted of a computer-based projection with restricted interactivity.

Further research needs to investigate whether our findings can be applied to younger or older children, other subject matter areas, and types of learning materials. Another limitation of the present study is that we did not controlled some moderating variables frequently encountered in animation research (Castro-Alonso et al., 2016), such as the quantity of elements depicted (number bias, i.e., number of images depicted is different in static and animated format), and the visualization format size (size bias, i.e., the animation is larger than the 12 static pictures). Future research could test whether eliminating/minimizing these biases (e.g., by designing all visualizations with the same dimensions) actually influence the learning outcomes. In this study, it was demonstrated that even children with high spatial abilities failed to effectively learn from static pictures. Further research should examine the effect of some external supports considered as helpful in adults (e.g., arrows-indicating motion; Imhof et al., 2013) on children mental animation abilities. Previous studies (e.g., Jarodzka et al., 2010; Mehigan et al., 2011) showed that the way of gazing at the external visualizations is strongly related to individual differences. It would be interesting therefore to employ eye tacking measurements to assess how children with different levels of spatial abilities gaze at animations and static pictures while learning.

CONCLUSION

In sum, these results suggest caution in the use of static pictures to convey dynamic information to young children. The static format is considered as the basic visual tool to communicate explicit visual movement may, but this study offers no reason to conclude that static format inherently provides more educational value than animation format. The difficulty to learn from static pictures is noticeable among both low and high spatial abilities children. In the end, casting more light on the way in which children use static and dynamic information will hopefully provide valuable input to teaching, learning, and the design of effective learning materials.

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 parents were required to consent to the inclusion of their child in the study and provide basic information on the child's developmental history. The study was conducted according to the Declaration of Helsinki and fully approved the Sfax University Ethics Committee (approval code CPP 0076/2017). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

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

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