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Original article

# Relationship between mode of sport training and general cognitive performance

Erik Chih-Hung Ch[a](#page-0-0)ng<sup>a</sup>, Chien-Heng Chu<sup>[b](#page-0-1)</sup>, Costas I. Karageorghis<sup>[c](#page-0-2)</sup>, Chun-Chih Wang<sup>b</sup>, J[a](#page-0-0)ck Han-Chao Tsai<sup>a</sup>, Yung-Shun Wang<sup>[d](#page-0-3)</sup>, Yu-Kai Chang [b,](#page-0-1)[\\*](#page-0-4)

<span id="page-0-0"></span><sup>a</sup> *Institute of Cognitive Neuroscience, National Central University, Taoyuan County 32001, Taiwan, China*

<span id="page-0-1"></span><sup>b</sup> *Graduate Institute of Athletics and Coaching Science, National Taiwan Sport University, Taoyuan County 33371, Taiwan, China*

<span id="page-0-2"></span><sup>c</sup> *Department of Life Sciences, Brunel University London, Middlesex UB8 3PH, UK*

<span id="page-0-3"></span><sup>d</sup> *Institute of Neuroscience, National Yang-Ming University, Taipei 11221, Taiwan, China*

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#### **Abstract**

*Purpose*: To investigate whether athletes who engage in different modes of sports training correspondingly exhibit different patterns of performance on general cognition tasks.

*Methods*: Sixty participants were recruited into an endurance, motorically complex, or control group, and were administered a series of physical tests and neuropsychological assessments.

*Results*: Athletes in the endurance group demonstrated the highest levels of cardiovascular fitness and those in the motorically complex group exhibited the highest levels of motor fitness. Nonetheless, no differences in cognitive performance were observed between the 3 groups.

*Conclusion*: These findings indicate that the mode of sport training, which results in either high cardiovascular or high motor fitness, bears no relationship to measures of general cognition in elite athletes. The present findings suggest that coaches and athletic trainers should be encouraged to monitor athletes' stress levels during training in order to maximize the beneficial effects of such training on general cognitive performance. © 2017 Production and hosting by Elsevier B.V. on behalf of Shanghai University of Sport. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

*Keywords:* Cognitive function; Executive control; Expert; Motor fitness; Physical fitness; Sport

## **1. Introduction**

Recent research has provided promising evidence for the positive relationship between exercise and cognition across the lifespan. $1-4$  In particular, studies that employed a cross-sectional design have indicated that people with higher fitness levels or those participating in habitual physical activity exhibit superior cognitive functions when compared to those with lower fitness levels, or those who exercise infrequently[.5,6](#page-5-1) Similar results have been reported in studies employing longitudinal designs, which have indicated that long-term exercise training and improved fitness levels are associated with better cognitive functions or a delay in age-related cognitive decline.<sup>7</sup>

<span id="page-0-4"></span>Peer review under responsibility of Shanghai University of Sport. Corresponding author.

*E-mail address:* [yukaichangnew@gmail.com](mailto:yukaichangnew@gmail.com) (Y.-K. Chang)

Meta-analyses have examined the possible moderator of exercise effects on cognition and have identified mode of exercise or training, age, and the type of cognitive task that is employed.<sup>8</sup> Most studies have addressed endurance or aerobic-type exercise and the corollary cardiovascular fitness effects on cognitive functions. Chaddock et al.<sup>5</sup> demonstrated that pre-adolescent children with high cardiovascular fitness levels exhibited superior memory performance when compared to those with low fitness status.Accordingly, Netz et al.<sup>6</sup> reported that older adults with moderate levels of cardiovascular fitness performed better in global cognitive functions when compared to those with lower fitness. The prominence of cardiovascular fitness has been positively associated with specific aspects of brain anatomy that are implicated in cognitive processes; these include hippocampal volume, basal ganglia volume, and neural functional connectivity. $9,10$ 

Other activity modes that require a high level of motor control (e.g., gymnastics and martial arts) can improve both physical fitness (e.g., cardiovascular capacity, muscular strength, and mus-

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cular duration) and motor fitness (e.g., power, agility, balance, and flexibility), which might have a bearing on cognition, beyond the effects attributable to enhanced cardiovascular fitness. Crosssectional studies have indicated that not only cardiovascular fitness but also muscular strength, agility, balance, motor coordination, and flexibility were associated with improvements in multiple cognitive functions in older adults<sup>11</sup> and children.<sup>12</sup> Further, a functional magnetic resonance imaging (fMRI) study showed that individuals with higher motor fitness exhibited higher levels of activation in certain brain regions (e.g., frontoparietal network) during cognitive tasks, suggesting a link between participation in a complex motor tasks or fitness training and cognition.<sup>11</sup> Nonetheless, given that only a few such studies have examined the effects of training modality on cognition, there is an insufficient evidence base with which to arrive at any firm conclusion.

With intense and prolonged training for competitive sport, athletes who reach the elite level are generally characterized by high physical and motor fitness. A reasonable assumption is that such athletes would exhibit adaptations in a range of cognitive functions. Indeed the expert performance approach hypothesis holds that when compared to non-experts, athletes with a high level of expertise should show superior outcomes across a range of sport-specific cognitive domains (e.g., decision making, declarative memory, perception, and visual searching capacity), with sports demanding high levels of coordination showing the most superior outcomes[.13,14](#page-6-0) Nevertheless, whether the effects of sports expertise might transfer from a sport-specific domain to a general cognitive domain has not been the topic of systematic investigation, albeit that initial findings do appear promising[.15,16](#page-6-1) Using the Delis–Kaplan Executive Function System (D-KEFS) test battery, Vestberg et al.<sup>15</sup> reported that both high and low division players displayed superior general cognitive performances compared to control groups, whereas higher division players showed additional improvements. Chaddock et al.<sup>16</sup> also examined sports expertise and general cognition, as assessed by a virtual reality street-crossing paradigm. They observed that Division I athletes had fewer collisions and faster processing speeds than non-athletes. While these recent studies provided some encouraging initial evidence regarding levels of athletic experience, it is not yet clear whether exposure to different types of sport may also influence general cognitive functions.

The purpose of the present study was to investigate the differences between types of sport (i.e., a sport with longduration/simple motoric skills *vs.* a sport involving complex motor skills) on general cognition in high-level athletes. We drew upon athletes who were accomplished in marathon running (endurance sport) and Wushu (a Chinese routine-based martial art involving a series of complex motor skills), given that we expected elite marathon runners to be endowed with high cardiovascular fitness, and professional martial artists to be endowed with cardiovascular fitness and high motor fitness. We hypothesized that both sports expertise groups would perform better when compared to a control group who were infrequent exercise participants, and sport expertise would influence cognitive performance differentially; the Wushu athletes would exhibit superior cognitive functions.

## **2. Methods**

#### *2.1. Participants*

Sixty college students (42 males,  $21.12 \pm 1.37$  years; 18 females,  $21.78 \pm 1.47$  years) were recruited from Taoyuan, Taiwan, China. All participants met the criteria of being free of cardiovascular, pulmonary, and metabolic diseases, as well as any mental disorders. They were screened using a demographic ques-tionnaire [\(Table 1\)](#page-2-0), their medical history, and the Physical Activity Readiness Questionnaire (PAR-Q).<sup>13</sup> Participants in the endurance group were elite athletes involved in marathon running while those in the motorically complex group were elite athletes involved in Wushu training. Control group participants engaged infrequently in exercise/recreational activity. Athletes in both sport groups had reached either national or international level in their respective disciplines and engaged in intensive training for at least 6 months prior to their recruitment into the study. Participants were required to read and sign an informed consent form.And this study was approved by the Institutional Ethics Committee of the National Taiwan Sport University.

#### *2.2. Cardiovascular fitness assessment*

Cardiovascular fitness is one of the main components of physical fitness and has been linked to cognitive performance. The peak oxygen consumption  $(VO<sub>2peak</sub>)$  for each participant was assessed using the Bruce Treadmill Protocol, which is a maximal graded exercise test (GXT). Each participant was required to undergo the fitness test on a motorized treadmill (h/p/cosmos airwalk, Traunstein, Germany). Several criteria were applied in determining each participant's maximal cardiovascular capacity including (a) a plateau in heart rate with increasing exercise intensity, (b) a respiratory exchange ratio above 1.15, (c) rating of perceived exertion on Borg's original RPE scale of 17 or above.

# *2.3. Muscular, muscular endurance, and flexibility assessment*

Other physical fitness components pertaining to muscular strength, muscular endurance and flexibility were assessed following exercise testing guidelines.<sup>17</sup> Specifically, muscular strength was assessed using a handgrip dynamometer for each hand. Muscular endurance was assessed using a protocol that entailed 60 s press-ups (male), 60 s bent-knee press-ups (female), as well as both 30 s and 60 s abdominal curl-ups. A sit-and-reach test was conducted using a flexometer to measure lower back and hamstring flexibility. Body composition was assessed by means of body mass index (BMI) as well as bioimpedance spectroscopy techniques (InBody 3.0 DS12B887; Biospace Co. Ltd., Seoul, Korea) with which percentage body fat mass was calculated.

# *2.4. Agility and power of motor fitness assessment*

In regard to motor fitness, emphasis was placed upon 2 components: agility and power. These were assessed using a T-test and a vertical jump test, respectively.<sup>18</sup> In the T-test, each participant was required to run as fast as possible to 4 cones that were arranged in a "T" formation. In the vertical jump, each

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Table 1

Descriptive data for participants' demographic and physical characteristics across 3 groups (mean ± SD).



Abbreviations: BMI = body mass index; Muscular endur./press-ups/CCU 30-s/CCU 60-s = muscular endurance/press ups/crunch curl-ups for 30 s/crunch curl-ups for 60 s; Training years = number of years engaged in sport training; WAIS-III = Wechsler Adult Intelligence Scale, 3rd ed.<sup>19</sup>

participant jumped as high as possible from a static position to facilitate assessment of their explosive strength.

### *2.5. Intelligence test*

We applied digit span and picture completion tests from the Wechsler Adult Intelligence Scale (WAIS-III, 3rd ed.) that was designed to identify multiple intelligence quotients in adults.<sup>19</sup> In the digit span test, each participant was asked to immediately repeat a series of digits presented by an experimenter (e.g., 7, 2, 8, 6), the length of the list would increase once the participant successfully repeated the list (up to 9 digits), and the longest digit number was recognized as their digit span. Each participant repeated the list in the given order or reverse order, and this was referred to as a "forward digit-span task" or a "backward digit-span test", respectively. The digit-span scores used for analysis were standardized (*z*) scores of the sum of the forward and backward digit-span tasks. During picture completion tests, each participant was asked to identify an item missing from a series of 20 pictures. These 2 subsets of WAIS-III represented the working memory and perceptual organization, respectively.

## *2.6. Neuropsychological assessment*

The primary outcome variable was cognitive function as assessed by several cognition-related measurements: Stroop test, Wisconsin Card Sorting Test (WCST), and Tower of London Task.

#### *2.6.1. Stroop test*

The Stroop test is a widely used neuropsychological assessment of perceptual speed and executive function and has been employed in exercise–cognition research.<sup>20,21</sup> Participants were requested to verbalize the 50 stimulus words (10 rows  $\times$  5 columns) that were presented in 5 conditions: Stroop congruent, Stroop word, Stroop square, Stroop neutral, and Stroop incongruent[.16](#page-6-2) The Stroop congruent condition entailed the presentation of names of colors printed in the same color as the name. For the Stroop word, the stimuli were names of colors written in black ink. For the Stroop square, the stimuli were rectangles presented in color. For the Stroop neutral, the stimuli were non-color-related words written in colored ink (e.g., tea, telephone, and staple). For the Stroop incongruent, the stimuli were the names of colors printed using a different color to the name (e.g., "RED" printed in green ink). During the test, each participant was instructed to name the color of each stimulus word as fast and as accurately as possible. Each participant was required to make a further attempt when errors were made.

# *2.6.2. WCST*

The WCST is a leading neuropsychological assessment of the shifting aspect of executive functions[.22,23](#page-6-7) The WCST: Computer Version 4 (Research Edition) was used. The WCST involved 4 key cards and 128 response cards that can be categorized based upon color (i.e., red, green, yellow, and blue), shape (i.e., triangle, star, cross, and circle), or number (i.e., 1, 2, 3, and 4). The task required the respondent to determine how

the response card corresponded with one of 4 key cards based upon its potential match characteristics (by pressing the F, G, H, or J keys on a computer keyboard). The computer provided the immediate feedback "Correct" or "Incorrect" after participants performed each response card trial to identify whether the card was correctly matched. The sorting category (i.e., color, shape, or number) changed after 10 consecutive correct sorts. The WCST was terminated after the participant either successfully performed 6 categories or completed 128 response cards. Generally, participants were able to complete the test administration within 20 min. The variables used in the statistical analyses were indices of categories completed, total correct, perseverative errors, perseverative response, conceptual level response, non-perseverative error, and failure to maintain set.

# *2.6.3. Tower of London TaskDX*

A version of the Tower of London Task<sup>DX</sup> (ToL Task) was used in this study. The ToL Task is a widely administered neuropsychological assessment for measuring the planning aspects of executive functions.TheToLTask consists of 2 identical wooden boards (30 cm  $\times$  7 cm  $\times$  10 cm), one for the participant and one for the experimenter, and 2 sets of 3 beans (blue, green, and red). Each board consists of 3 vertical pegs with graded heights, where the longest, middle, and shortest peg can hold 3, 2, and 1 bean, respectively. Each participant was asked to move beans as few times as possible from the starting configuration to one of 10 goal configurations while not violating the rules.<sup>24,25</sup> Administration of the ToL Task took 20 min. Total correct scores and total move scores were derived for statistical analysis given that these scores have been found to be influenced by aerobic and resistance (anaerobic) exercises. $24,25$ 

#### *2.6.4. Experimental procedure*

Participants visited the laboratory individually for 3 sessions, each of 90 min. All sessions were completed within 2 weeks and separated by at least a 2-day interval. During the first session, each participant completed an informed consent form as well as demographic, medical history, PAR-Q, and International Physical Activity Questionnaire  $(IPAQ)^{26}$  to identify whether they met the inclusion criteria. Resting heart rate was assessed after each participant sat quietly in a comfortable chair for 20 min. Participants who met the inclusion criteria were then instructed to perform the cognitive tasks of WAIS-III, Stroop test, WCST, and ToL Task. Participants in the second and third sessions either had their cardiovascular fitness assessed using the GXT or were administered other physical and motor fitness tests. In the third session, there was a semistructured interview to assess participants' views on their sport training and this was followed immediately by the test phase of the study.

# *2.7. Statistical analyses*

A between-subject design was applied. One-way ANOVA was used to evaluate differences across groups (i.e., endurance, motorically complex, and control). A mixed-model 3  $(group) \times 5$  (condition) ANOVA was employed for the Stroop test. One-way ANOVA was used to detect the differences across

groups in other cognitive measures including WCST and the ToL Task. The identification of significant differences on physical and motor fitness, Stroop test, WCST, and ToL Task among groups was followed by multiple comparisons that were Bonferroni-adjusted.

# **3. Results**

#### *3.1. Participant characteristics*

There was no significant difference  $(p > 0.05)$  across groups in regard to age, height, gender, father and mothers' education level, and socio-economic status of the family. In addition, no significant difference  $(p > 0.05)$  across groups was observed in digit span and picture completion tests of WAIS-III. These results suggest a degree of homogeneity across the 3 groups of participants in terms of demographic data [\(Table 1\)](#page-2-0).

## *3.2. Sport characteristics*

In regard to sport characteristics, there were significant differences in the number of years engaged in sport training, daily training hours, and daily hours of vigorous training (all at *p* < 0.001). *Post hoc* analyses revealed that both sport groups had a longer training year and more daily hours of training than those in the control group. Further, the motorically complex group had the most daily training hours across 3 groups [\(Table 1\)](#page-2-0).

#### *3.3. Physical characteristics measures*

Results of the measures across groups revealed that there were significant differences in VO<sub>2peak</sub>, muscular endurance, flexibility, agility, and power (all at  $p < 0.001$ ), as well as % body fat mass and BMI (both at *p* < 0.05). *Post hoc* analyses indicated that the endurance group had the highest  $VO<sub>2peak</sub>$  and lowest body composition (BMI and % body fat mass), followed by the motorically complex group, and the control group had the lowest VO2peak and highest body composition. Regarding muscular endurance (press-ups, 30 s and 60 s crunch curl-ups), flexibility, agility, and power, the motorically complex group recorded the highest values, followed by the endurance group, and the control group had the lowest values (all at  $p < 0.001$ ). A similar trend was observed for muscular strength, although this did not reach statistical significance  $(p > 0.05)$  [\(Table 1\)](#page-2-0).

#### *3.4. Cognitive performance*

[Table 2](#page-4-0) contains descriptive data for cognitive performance outcomes. Regarding the Stroop test, a mixed-model ANOVA revealed no significant Group × Condition interaction or main effect of group; whereas there was a significant main effect of Stroop test condition  $(F = 266.5, p < 0.01)$ . *Post hoc* analyses indicated that the Stroop incongruent condition was associated with the longest response time, and following this were the Stroop neutral, Stroop square, and then Stroop word, with no significant differences across the latter 3 conditions, while Stroop congruent exhibited the shortest response time.

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Table 2

Descriptive data for participants' cognitive performances across control, endurance, and motorically complex groups (mean ± SD).

Variable	Control $(n=20)$	Endurance $(n=20)$	Motorically complex $(n=20)$	Total $(n = 60)$
Stroop congruent (s)	$16.78 \pm 4.07$	$17.50 \pm 4.22$	$15.37 \pm 2.15$	$16.55 \pm 3.65$
Stroop word (s)	$17.81 \pm 3.25$	$19.79 \pm 4.28$	$17.88 \pm 2.78$	$18.49 \pm 3.56$
Stroop square $(s)$	$20.83 \pm 4.22$	$22.43 \pm 4.32$	$21.00 \pm 2.99$	$21.43 \pm 3.89$
Stroop neutral (s)	$22.20 \pm 3.74$	$24.26 \pm 4.61$	$22.76 \pm 3.58$	$23.09 \pm 4.03$
Stroop incongruent (s)	$34.33 \pm 8.25$	$36.83 \pm 8.74$	$34.31 \pm 6.26$	$35.16 \pm 7.78$
<b>Wisconsin Card Sorting Test</b>				
Categories completed	$5.85 \pm 0.49$	$5.45 \pm 1.32$	$5.60 \pm 1.19$	$5.63 \pm 1.06$
Total correct	$68.90 \pm 6.21$	$70.75 \pm 8.06$	$71.05 \pm 8.63$	$70.23 \pm 7.63$
Perseverative errors	$9.05 \pm 6.52$	$12.95 \pm 10.75$	$10.55 \pm 6.51$	$10.85 \pm 8.20$
Perseverative responses	$9.80 \pm 7.88$	$14.70 \pm 13.68$	$11.65 \pm 7.25$	$12.05 \pm 10.07$
Conceptual level response	$64.30 \pm 6.23$	$64.80 \pm 8.89$	$65.20 \pm 9.17$	$64.77 \pm 8.08$
Non-perseverative errors	$11.25 \pm 9.84$	$14.55 \pm 11.95$	$11.15 \pm 8.76$	$12.32 \pm 10.22$
Failure to maintain set	$0.35 \pm 0.67$	$0.70 \pm 1.30$	$0.55 \pm 0.89$	$0.53 \pm 0.89$
Tower of London Task <sup>DX</sup>				
Total correct scores	$4.55 \pm 2.04$	$4.10 \pm 2.47$	$2.90 \pm 2.27$	$3.85 \pm 2.33$
Total move scores	$28.45 \pm 12.56$	$28.10 \pm 16.08$	$37.55 \pm 16.43$	$31.36 \pm 15.51$

One-way ANOVA revealed no significant differences  $(p > 0.05)$ across the 3 groups in WCST and ToL Task performance.

# **4. Discussion**

The present study investigated whether elite athletes with high fitness levels exhibited superior performances on general cognition tests when compared to a recreationally active control group, and whether the type of sport that athletes participated in (endurance *vs.* motorically complex) had a bearing on cognitive performance.

As predicted, both sport groups demonstrated superior physical and motor fitness when compared to the control group. Specifically, marathon runners had the highest cardiovascular fitness and lowest percentage of body fat, whereas Wushu athletes exhibited the highest levels of local muscular endurance, flexibility, agility, and power. Interestingly, in contrast to our research hypothesis, there was no significant difference across the 3 groups for the battery of general cognitive tasks assessed in the present study.

Although the findings did not replicate those of previous exercise–cognition studies that demonstrated positive effects of fitness on cognitive function among non-sport populations,  $27,28$ our findings did support those of a small number of sportrelated studies[.29,30](#page-6-11) The latter studies indicate that the experiences of accomplished sports persons have limited influence on general cognition that is assessed under laboratory conditions. Helson and Starkes $30$  found that only domain-specific cognition rather than non-specific cognition could differentiate between expert and intermediate-level soccer players. Similarly, Lum et al[.29](#page-6-11) indicated that, compared to non-athletes, athletes with static (e.g., swimming) or dynamic (e.g., soccer) experience exhibited no difference in automatic orienting of general cognitive domain, but voluntary orienting and modulation of automatic orienting of sport-specific cognitive domain. Therefore, our findings indicate that whether level of expertise accounts

for specific aspects of general cognition remains a matter of considerable debate.<sup>31,32</sup>

In addition to the perceptual speed aspect of cognition (e.g., Stroop congruent, Stroop word conditions), the present study examined the executive control aspects of cognition using neuropsychological assessments (e.g., Stroop incongruent condition, WCST, and ToL Task), which adds to the existing knowledge base. The present findings fall in line with those of previous studies that demonstrated a Stroop interference effect (i.e., longer response times of Stroop incongruent condition compared to Stroop neutral condition) and a Stroop facilitation effect (i.e., shorter response time of Stroop congruent condition compared to Stroop neutral condition). Both Stroop effects are the consequence of multiple competitive cognitive processes during naming the color word and identifying the meaning of words.<sup>21,33</sup> Additionally, we applied the neuropsychological assessments recommended by Etnier and Chang<sup>22</sup> including the Stroop test, WCST, and ToL Task, in order to measure interferences, shifting, and planning aspects of executive control. These represent higher level cognitive functions that are responsible for goal-oriented behavior[.18](#page-6-4) However, whether these executive functions that relate to general cognitive domains could match the complexities of the sports environment and therefore be influenced by expert experiences has been the subject of debate[.34](#page-6-15) Given that meta-analytic reviews have indicated that in sport-related perception–cognitive domains, athletes exhibited better performances (e.g., greater accuracy, shorter attentional cuing time, faster processing speeds when responding to environmental stimuli, fewer fixations), $13,35$  the findings of the present study suggest that any beneficial effects on cognition might be associated with sport-specific cognitive domains rather than general cognitive domains, particularly executive function.

The failure to reveal any positive relationship between expertise in sports and general cognitive abilities may also be attributable to the dose–response trend involved between exercise and cognition, wherein extreme training doses would limit physiological and psychological functions[.36](#page-6-16) Sport-related training improves physical abilities (e.g., cardiovascular fitness and motor fitness); nonetheless, excessive physical training might cause physiological maladaptations and, in turn, offset the potentially beneficial effects of exercise on cognition. Several studies have indicated that excessive or highly intense training/exercise results in oxidative stress, which is an imbalance between reactive oxygen species and antioxidant defense systems. This results in disturbances in the normal redox state by producing peroxides and free radicals, and consequently leads to damage to proteins and lipids of the cell plasma. $37$ Oxidative stress has been linked to decreased cognition or increased cognitive decline symptoms, $38,39$  and research has further indicated that intense exercise can lead to oxidative stress in the brain, which in turn impairs basic information processes and executive cognitive performances[.40](#page-6-19) Through the semi-structured interviews, we found that the 2 athlete groups indicated that with prolonged high-intensity training, they often experienced burnout-related symptoms and high levels of fatigue. For example, athletes engaged in marathon training ran at least 25 km per day, while Wushu athletes endured 5 h of training per day with almost 3 h of anaerobic-type training. There is a possibility that the effects of overtraining offset the beneficial cognitive functions associated with exercise in the general population.

Second, the type of cognitive tasks employed should be carefully considered. While the current study applied multiple neuropsychological assessments, as suggested in the literature, $22$ these assessments only measure cognitive function in terms of information processing, interference, shifting, and planning aspects of cognition; notwithstanding this, the results were unable to be generalized to other aspects of cognition. Third, studies that have found positive associations between exercise participation and cognition have been examined predominantly in either older adults or pre-adolescents,<sup>5,11,12,41</sup> while the present study targeted young adults. Clearly, additional work is required to examine the other types of cognitive function, as well as populations of different ages in order to further understanding.

Some limitations warrant consideration while interpreting the current data. First, although the screening procedure was intended to ensure a level of homogeneity, as indicated by a lack of difference across a range of demographic variables across the 3 test groups (e.g., age, education, working memory, perceptual organization aspects of intelligence quotients, and parents' education), the cross-sectional design could not control for other factors that might influence cognition (e.g., level of sporting attainment). Longitudinal studies that adopt an idiographic approach are therefore recommended in examining the impact of intensive sport-related training on cognition.

# **5. Conclusion**

Athletes who engaged in contrasting training modalities did not exhibit any enhancements in general cognition when compared with a recreationally active control group. Given that only a few studies have examined the effects of sport-related training with reference to general cognition,<sup>15,16</sup> the present findings

highlight the necessity to initiate additional studies that address whether individuals with a superior fitness status or long-term engagement in sports training of different types (e.g., motoric *vs.* cognitive) show that their physical training activities have influenced their general cognition. It is also the case that athletes who have been engaged in long-term programs of mental training as part of their preparation for competitive sport might also exhibit enhancements in general cognition.

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## **Authors' contributions**

ECHC and CHC designed the study and oversaw the data collection; YKC designed the study, oversaw the data collection, analyzed the data, and wrote up the inital manuscript. CIK assisted with analysis of the data, as well as in the organisation and write-up of the manuscript. CCW, JHCT, and YSW collected the data. All authors played a part in the preparation of the manuscript at each stage of its development. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

# **Competing interests**

None of the authors declare competing financial interests.

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