Psychoneuroendocrinology (2014) 39, 214—224

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

Aerobic exercise interacts with neurotrophic factors to predict cognitive functioning in adolescents

Tatia M.C. Lee [a,b,c,d,*], Mark Lawrence Wong [a], Benson Wui-Man Lau [e], Jada Chia-Di Lee [f], Suk-Yu Yau [g], Kwok-Fai So [c,f,h]

[a] *Laboratory of Neuropsychology, The University of Hong Kong, Hong Kong*
[b] *Laboratory of Social Cognitive Affective Neuroscience, The University of Hong Kong, Hong Kong*
[c] *The State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong*
[d] *Institute of Clinical Neuropsychology, The University of Hong Kong, Hong Kong*
[e] *Department of Rehabilitation Science, The Hong Kong Polytechnic University, Hong Kong*
[f] *Department of Ophthalmology, The University of Hong Kong, Hong Kong*
[g] *Division of Medical Sciences, The University of Victoria, British Columbia, Canada*
[h] *GMH Institute of CNS Regeneration, and Guangdong Medical Key Laboratory of Brain Function and Diseases, Jinan University, Guangzhou, China*

Received 1 May 2013; received in revised form 17 September 2013; accepted 17 September 2013

KEYWORDS
Exercise;
Neurotrophic factors;
Cognition;
Neurogenesis;
Frontal regions;
Temporal regions

Summary Recent findings have suggested that aerobic exercise may have a positive effect on brain functioning, in addition to its well-recognized beneficial effects on human physiology. This study confirmed the cognitive effects of aerobic exercise on the human brain. It also examined the relationships between exercise and the serum levels of neurotrophic factors (BDNF, IGI-1, and VEGF). A total of 91 healthy teens who exercised regularly participated in this study. A between-group design was adopted to compare cognitive functioning subserved by the frontal and temporal brain regions and the serum levels of neurotrophic factors between 45 regular exercisers and 46 matched controls. The exercisers performed significantly better than the controls on the frontal and temporal functioning parameters measured. This beneficial cognitive effect was region-specific because no such positive cognitive effect on task-tapping occipital functioning was observed. With respect to the serum levels of the neurotrophic factors, a negative correlation between neurotrophic factors (BDNF and VEGF) with frontal and medial-temporal lobe function was revealed. Furthermore, the levels of BDNF and VEGF interacted with

* Corresponding author at: Laboratory of Neuropsychology, The University of Hong Kong, Room 656, The Jockey Club Tower, Pokfulam Road, Hong Kong. Tel.: +852 3917 8394; fax: +852 2819 0978.
E-mail address: tmclee@hku.hk (T.M.C. Lee).

http://dx.doi.org/10.1016/j.psyneuen.2013.09.019

exercise status in predicting frontal and temporal lobe function. This is the first report of the interaction effects of exercise and neurotrophic factors on cognitive functioning. Herein, we report preliminary evidence of the beneficial effects of regular aerobic exercise in improving cognitive functions in teens. These beneficial effects are region-specific and are associated with the serum levels of neurotrophic factors. Our findings lay the path for future studies looking at ways to translate these beneficial effects to therapeutic strategies for adolescents.

1. Introduction

The beneficial effect of aerobic exercise (exercise) on human cognitive functioning and mental well-being has been well documented. Evidence on the positive effects of exercise in protecting against age-related cognitive decline (Larson et al., 2006) and mood disturbances (Trivedi et al., 2011) has been consistent. In a meta-analysis, Colcombe and Kramer (2003) suggested that exercise could improve the performance of older adults on various cognitive tests, particularly on tests of executive functioning. Consistently, Smith et al. (2010) reviewed existing randomized-controlled trials on the effect of exercise on cognition and concluded that exercise was modestly effective in enhancing cognitive functions, including executive functions and memory. While there have been consistent findings on the beneficial effect of exercise on promoting healthy aging, its effect on younger populations has been equivocal (Guiney and Machado, 2013; Verburgh et al., 2013). Some studies have reported that regular exercise and better physical fitness were associated with better selective attention in healthy adolescents (mean age = 14.2 years) (Stroth et al., 2009), response inhibition in school-aged students (13—16 years) (Budde et al., 2008), and working memory in high school students (15—16 years) (Budde et al., 2010). On the other hand, a recent meta-analysis failed to identify any beneficial cognitive effect of chronic exercise among adolescents, which might be related to the small number of studies (Verburgh et al., 2013).

In parallel with increasing studies on the cognitive and affective effects of exercise, there has been a quest for knowledge regarding the neural underpinnings of the effect of exercise (van Praag, 2009; Smith et al., 2010). Exercise was previously considered in early literature as a part of an enriched environment, which promoted neurogenesis and cell proliferation in the dentate gyrus in mice (e.g. van Praag et al., 1999). Recent studies have furthered our understanding that exercise also affects the cerebral blood volume of the dentate gyrus (Pereira et al., 2007) and enhances the process of adult neurogenesis in the hippocampus (Kobilo et al., 2011). Rats that were reared in an enriched environment had been offered the opportunity to exercise showed increased cell proliferation and brain-derived neurotrophic factor (BDNF) mRNA expression in the dentate gyrus (Bechara and Kelly, 2013). Our recent animal studies (Yau et al., 2011b, 2012) examined the causal relationship between exercise and neurogenesis and observed that exercised rats exhibited enhanced neurogenesis in the hippocampus, and dendritic remodeling in hippocampal neurons was facilitated. Coupled with the neuronal changes induced by exercise, these rats showed reduced depression-like behavior and enhanced medial temporal function-spatial memory as measured by their performance on the Morris water maze test. Another animal study conducted by our group demonstrated neurogenesis in the frontal subventricular zone in mice (Lau et al., 2011). These exciting findings prompted this current study investigating the physiological and behavioral coupling of the effect of exercise on cognitive affective functioning in younger adults.

Neurogenesis in adult humans can be observed by studying the peripheral levels of neurotrophic factors that influence the development, proliferation, differentiation and regulation of new cells in the brain, particularly in neurogenic brain regions (e.g., dentate gyrus) (e.g. Cao et al., 2004). The brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF) are three potential candidates proposed to mediate the effects of exercise on the brain (Yau et al., 2011a). BDNF and IGF-1 are suggested to be involved in the regulation of exercise-induced benefits on hippocampal-dependent learning (e.g., Vaynman et al., 2004). In addition, IGF-1 and VEGF are involved in activating hippocampal neurogenesis and angiogenesis; when peripheral IGF-1 and VEGF are blocked, even after exercise, neurogenesis is suppressed (Trejo et al., 2001; Fabel et al., 2003).

Previous studies on the relationship between exercise and neurotrophic factors have been inconsistent. For example, Heyman et al. (2012) observed that among young adults who were exposed to intensive training in cycling, their BDNF levels increased from baseline after a 60-min exercise protocol. Positive associations between exercise and BDNF (Yarrow et al., 2010), IGF-1 (Schwarz et al., 1996) and VEGF (Kraus et al., 2004) have also been reported. However, some studies have observed that exercise was associated with a lowering of the level of these neurotrophic factors. For example, serum levels of BDNF were found to negatively correlate with cardiorespiratory fitness assessed using the maximal treadmill test (Jung et al., 2011). Moreover, negative associations were reported between exercise and BDNF (Currie et al., 2009), IGF-1 (Walker et al., 2004), and VEGF (Gu et al., 2004). These neurotrophic factors might be potential mediators of exercise and cognition; however, their relationship with exercise remains unclear.

Extending our findings obtained in previous animal studies, this study verified the relationship between regular exercise and cognitive performance in younger brains. To the best knowledge of the authors, no existing study has fully addressed the relationships between exercise dosage, cognitive functions, and neurotrophic factors in human adolescents, despite the promising data from recent adolescent animal studies (e.g. Hopkins et al., 2011; Cetinkaya et al., 2013). While human brain continues to develop from adolescence through young adulthood, any factors promoting its growth or preventing its deterioration in this critical period

may provide invaluable information to both academia and the health community.

In addition, the use of cognitive tasks that specifically tap into the functions of the medial-temporal and frontal areas of the brain showed that structural changes (neurogenesis) induced by exercise (Smith et al., 2010; Voss et al., 2011; Yau et al., 2011a) were employed in this study. Based on our previous animal data (Lau et al., 2011; Yau et al., 2011b, 2012), we hypothesized that exercise was associated with a significant better performance on cognitive tasks that assessed frontal and medial-temporal lobe function, and thus, the beneficial effect would not extend to functions served by occipital regions. To understand the biochemical underpinnings of the relationship between exercise and cognitive functioning, we examined the relationship between exercise and the serum levels of neurotrophic factors. We hypothesized that exercise would correlate with the levels of neurotrophic factors, and furthermore, while exercise dosage is positively correlated with enhanced cognitive functions (frontal and medial-temporal), such a relationship could be further explained by the serum levels of neurotrophic factors.

2. Methods

2.1. Participants

A total of 91 healthy, right-handed, Cantonese-speaking Chinese subjects participated in this study, which was approved by the Institutional Review Board of the University of Hong Kong. Written informed consent was obtained prior to the study. Among these 91 participants, 45 of the subjects were adolescent exercisers who engaged in regular exercise and the other 46 matched-controls did not exercise regularly. The exercisers were recruited from the Hong Kong Sports Institute where they received intensive training on rowing, swimming, running (>1000 m) or triathlon for at least two months prior to this study. The controls were recruited from the community using posters, e-mails and word of mouth. All of the participants were screened for their health conditions and exercise dosage. They were excluded if they had any history of medical or mental conditions affecting cognitive and/or emotional functioning. The exercise and control groups were matched based on their intelligence, which was measured using the Standard Progressive Matrices (Raven et al., 2000), handedness as measured using the Lateral Dominance Test (Harris, 1958) and affective state as measured using the Chinese Affect Scale (Cheng, 2004). Their psychomotor speed was measured using the Finger Tapping Test (Reitan and Wolfson, 1985) and set as a covariate in the analyses.

2.2. Design and procedures

This study adopted a between-group design to compare the cognitive functions and serum levels of neurotrophic factors (BDNF, IGF-1 and VEGF) between exercisers and controls. There was also a moderation analysis on the role of exercise dosage on the relationship between the serum levels of neurotrophic factors and the cognitive functions in all participants. The participants were first briefed on the research background and provided their written informed consent. They then participated in the screening session and testing session. All of the testing materials and instructions were administered in the Chinese language. During the screening session, the subjects completed measurements on their demographics and health conditions, exercise dosage, emotional status and intelligence. Eligible participants proceeded to take a blood test and then began the testing session, which included cognitive tasks that tapped the frontal and medial temporal lobe function. Two sets of test orders were used to control for the ordering effect.

2.3. Measurements

2.3.1. Exercise dosage

Several measurements were used to assess the participants' regular exercise habits. We used the leisure activities domain score in the International Physical Activity Questionnaire (IPAQ) (Chinese version) to measure the amount of exercise dosage in the past year and the annual average since age 11 (Craig et al., 2003; Qu and Li, 2004). The total amount of exercise dosage was calculated by multiplying the metabolic equivalent (MET) score for the physical activity engaged, with the time spent on that activity. Scoring details and calculations were determined according to the IPAQ scoring protocol guidelines (IPAQ Research Committee, 2005). The Chinese version of IPAQ also has satisfactory psychometric properties (Inter-class correlation = .927) (Qu and Li, 2004). Among the exercisers, their training duration in the Hong Kong Sports Institute and the exercise training duration prior to entering the Institute (for the same type of sport trained in the Institute) were also measured as variables indicating their exercise dosage.

2.3.2. Serum levels of BDNF, IGF-1 and VEGF

A trained research nurse drew 3 × 200 μl of blood from the participants to assess the serum concentration of BDNF, IGF-1 and VEGF. The serum concentrations of these factors were assayed using the commercial enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems Inc., US).

2.3.3. Neuropsychological assessment

A battery of tests which were reported to be associated with specific brain functions of the frontal and medial-temporal lobe was administered to all of the participants on a one-to-one basis. Specifically, the Stroop Color-Word Test (Stuss et al., 2001), the Wisconsin Card Sorting Test (Stuss et al., 2000), and the dual task (Baddeley et al., 1997) were tests of cognitive processes subserved by the frontal lobe. The spatial memory task and the spatial associative learning tasks were tests of cognitive processes subserved by the medial-temporal lobe (Howard et al., 2005). A control task tapping occipital function (Boyntona et al., 1999) was also administered to test for the specific neural effect of exercise.

1. The Stroop Color-Word Test (Lee and Chan, 2000) measured cognitive inhibition and control by requiring the participants to inhibit the semantic interference introduced by the semantic meaning of the color words. Three subtests were administered, namely color dots, color of non-color words, and color words that conflict with the color in which they were presented. Reaction times (in

seconds) for naming the stimuli were recorded separately for these subtests. The interference score measured cognitive control and inhibition was calculated by the different reaction times in the color-dots vs. the color-word conditions.

2. The computerized Wisconsin Card Sorting Test, WCST (Heaton et al., 1993) measured cognitive flexibility by requiring the participants to match 128 stimulus cards with the corresponding target card in response to the administrator's feedback. The matching rule changed on a predetermined order unknown to the participants.
3. The dual task measured multitasking by requiring the participants to attend and respond to changes in the parameter of circles (luminance) presented in the right and left visual fields. There were 60 trials in this task. In each trial, two circular fields presented concurrently on the computer screen might change in luminance. The participants had to attend to both circular fields. In each circular field, the 1 s baseline luminance was followed by the 1 s target luminance. The participants were required to compare the target luminance level with that of the previous one, and to respond if the two luminance levels were different. Accuracy and reaction time were the outcome indices.
4. The spatial memory task required the participants to recall as promptly as they could on the spatial location of the objects previously presented to them. There were seven trials in this task. In each trial, the participants were required to learn the spatial location of six target boxes presented one after the other (3 s presentation with a 0.5 s backward mask). Then, foil—target pairs were presented, one at a time. The participants were required to identify the correct targets from the foils. Accuracy and reaction time were the variables indicating their ability in spatial recognition memory.
5. The spatial associative learning task measured spatial associative memory by requiring the participants to match the location of an object previously presented. There were five blocks in this task. In each block, during the learning phase, a number of objects were presented, one at a time, in various locations on the screen (3 s presentation with 1 s backward mask). After the learning phase, each object was presented in the center of the screen and the participants were required to point out the correct location of the object. Accuracy and reaction time were the outcome indices of this test.
6. The contrast discrimination task ascertained primary visual cortex function by requiring the participants to discriminate the luminance contrasts. There were 120 trials in this task. In each trial, a dot fixation was presented for 0.5 s. Then, two black-and-white checkerboards were presented in a pair for 2 s. The participants were required to judge which of the two checkboards had a greater luminance contrast.

2.4. Statistical analysis

Independent sample t-test/χ^2-test was the first test used to explore the baseline group differences, e.g., age, sex, body mass index (BMI), intelligence, handedness, psychomotor speed and emotional status. We then proceeded to compare the effect of group differences on exercise dosage, serum level of BDNF, IGF-1, and VEGF and cognitive functions with the control of psychomotor speed using a one-way analysis of variance model with the baseline differences controlled. Correlational analyses (Pearson's r) were used to assess

Table 1 The effect of between-group differences on demographics, blood and exercise variables.

	Exercisers	Controls	t or χ^2	p Value
N	45	46		
Age (years)	16.49 ± 2.04	16.78 ± 2.04	0.686	.494
Sex (male)	29	21	3.245	.072
Body mass index	20.90 ± 2.19	20.29 ± 2.48	−1.248	.215
Education (years)	10.78 ± 2.00	10.54 ± 1.75	−0.596	.533
Handedness (LDT score)	5.42 ± 1.41	5.74 ± 0.53	1.427	.570
Psychomotor speed (FTT score)				
Intellectual functioning (Raven score)	53.49 ± 5.57	53.37 ± 5.73	−0.101	.920
Positive affect (CAS score)	35.09 ± 7.19	33.24 ± 6.32	−1.293	.199
Negative affect (CAS score)	18.75 ± 6.55	18.47 ± 6.38	−0.207	.837
Exercise				
MET (previous year)	156.09 ± 82.61	29.12 ± 31.90	9.712	<.001***
MET (annual average from age 11 years)	124.60 ± 80.29	32.35 ± 40.40	6.946	<.001***
Neurotrophic factors				
BDNF	64.80 ± 45.92	102.01 ± 30.52	4.428	<.001***
IGF-1	99.71 ± 20.20	104.28 ± 22.82	0.975	.332
VEGF	72.00 ± 58.11	102.32 ± 66.17	2.137	.036*

LDT = Lateral Dominance Test; FTT = Finger Tapping Test; Raven = Standard Progressive Matrices; CAS = Chinese Affect Scale; MET = Metabolic Equivalent of Task (vigorous activities); BDNF = brain-derived neurotrophic factor; IGF-1: Insulin-like growth factor-1; VEGF: vascular endothelial growth factor.

* $p < .05$.
** $p < .01$.
*** $p < .001$.

the relationship between the serum levels of neurotrophic factors with exercise dosage.

Sequential regression analyses were used to test if the exercise dosage interacted with the serum level of neurotrophic factors in affecting cognitive functions. The participants' demographics were entered in the first step. Their group assignment (exercisers versus controls) and serum levels of neurotrophic factors were entered in the second step. Due to co-linearity, BDNF and VEGF were centered (by subtracting the group mean values). The last step included an interaction term (exercise dosage $\times$ serum level of neurotrophic factors). The outcome variables were the aforementioned variables for the neuropsychological assessments. All of the statistical analyses were performed using the Statistical Package for the Social Sciences software (IBM SPSS 19.0), and statistical significance was determined by a p value $< .05$.

3. Results

3.1. Demographic variables

The exercisers and control subjects were matched in age, sex, BMI, years of education, handedness, and intelligence as well as positive and negative affect ($p > .05$) (Table 1). We then proceeded to compare the groups' exercise dosage and serum levels of neurotrophic factors. For exercise dosage, the exercisers demonstrated a higher level of MET compared to the controls in the previous year ($t(89) = 9.712$, $p < .001$) and the annual average since age 11 ($t(89) = 6.946$, $p < .001$). Six participants (4 exercisers) did not volunteer for the blood test. The exercisers had significantly lower levels of BDNF ($t(83) = 4.428$, $p < .001$) and VEGF ($t(89) = 2.137$, $p = .036$). However, no significant group difference in the IGF-1 levels was observed ($p > .05$).

3.2. Exercise and cognitive functions

The exercisers, relative to the controls, showed a much better performance on cognitive tasks that assessed the frontal and medial-temporal lobe function. These findings were not present when the contrast discrimination task tapping occipital functioning was used (Table 2).

To control for the exercisers' enhanced psychomotor skills, the Finger Tapping Task was measured ($t(89) = 3.66$, $p < .001$). Performance on the Finger Tapping Task was made a covariate in the ANCOVA model. For tasks associated with frontal lobe function, the exercisers demonstrated a better performance in the Stroop Color-Word Test, including a shorter reaction time in the neutral word conditions ($F_{2,90} = 7.443$, $p = .008$) and color word conditions ($F_{2,90} = 4.424$, $p = .038$). In the Wisconsin Card Sorting Test (WCST), compared with the controls, the exercisers exhibited a higher accuracy rate ($F_{2,90} = 6.716$, $p = .018$) used fewer trials to complete the test ($F_{2,90} = 7.098$, $p = .009$), made more conceptual responses ($F_{2,90} = 4.900$, $p = .030$) and provided fewer non-perseverative errors ($F_{2,90} = 8.918$, $p = .004$). No significant group difference was observed in the dual task ($p > .05$) though we saw a trend that exercisers had higher overall than the controls.

The exercisers also performed better on the cognitive tasks that were associated with medial-temporal functions. In the spatial associative learning task, the exercisers had a higher memory score ($F_{2,90} = 6.712$, $p = .011$) and accuracy ($F_{2,90} = 3.293$, $p = .016$). No significant difference was observed on the spatial recognition test though there was a trend showing better overall accuracy among the exercise group ($p > .05$).

3.3. Relationships between exercise and neurotrophic factors

The correlation coefficients among exercise and neurotrophic factors are presented in Table 3. Exercise dosage in the previous year (MET-last year) correlated significantly with a lower level of BDNF ($r(85) = -.293$, $p = .007$). The annual exercise dosage from age 11 (MET after 11) correlated significantly with a lower level of BDNF ($r(85) = -.417$, $p < .001$) and VEGF ($r(85) = -.251$, $p = .028$). Among the

Table 2 The effect of significant between-group differences on cognitive functions.

	Exercisers ($n = 45$)	Controls ($n = 46$)	t or χ^2	p Value	F	p Value
Frontal functions						
FTT: Number of taps	61.09 ± 4.66	54.43 ± 11.29	-3.661	$<.001^{***}$		
Stroop: Dot (rt)	10.76 ± 1.68	11.77 ± 2.11	2.431	$.017^{*}$	3.661	.059
Stroop: Neutral word (rt)	12.12 ± 1.90	13.79 ± 2.81	3.225	$.002^{**}$	7.443	$.008^{**}$
Stroop: Color word (rt)	18.10 ± 4.51	20.40 ± 5.93	2.075	$.041^{*}$	4.424	$.038^{*}$
WCST: Accuracy	81.03 ± 6.17	77.38 ± 7.37	-2.414	$.018^{*}$	6.176	$.015^{*}$
WCST: Number of trials	90.18 ± 17.13	100.20 ± 18.37	2.538	$.013^{*}$	7.098	$.009^{**}$
WCST: Conceptual response rate	0.77 ± 0.09	0.72 ± 0.10	-2.274	$.026^{*}$	4.900	$.030^{*}$
WCST: Non-perseverative error rate	0.10 ± 0.04	0.13 ± 0.05	2.664	$.009^{**}$	8.918	$.004^{**}$
Medial temporal functions						
SAL: Memory score	0.81 ± 0.11	0.75 ± 0.13	-2.103	$.038^{*}$	6.712	$.011^{*}$
SAL: Overall accuracy	0.87 ± 0.06	0.84 ± 0.08	-2.018	$.047^{*}$	3.293	$.016^{*}$

Stroop = Stroop Color-Word Test; rt = reaction time; WCST = Wisconsin Card Sorting Task; SAL = Spatial Associative Learning Task.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

Table 3 Relationships between exercise and neurotrophic factors.

	1	2	3	4	5	6
1. BDNF	1					
2. IGF-1	.046	1				
3. VEGF	.461***	.029	1			
4. MET last year	−.293**	−.094	−.149	1		
5. MET after age 11 years	−.417***	−.162	−.251*	.859***	1	
6. Training in HKSI	−.317**	−.308**	−.169	.415***	.400***	1

BDNF = brain-derived neurotrophic factor; IGF-1: Insulin-like growth factor-1; VEGF: vascular endothelial growth factor; MET = Metabolic Equivalent of Task (vigorous activities); HKSI: Hong Kong Sports Institute.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

exercisers, the duration of training in the Sports Institute correlated significantly with a lower level of BDNF ($r(85) = -.317$, $p = .003$) and IGF-1 ($r(85) = -.308$, $p = .004$).

3.4. The role of neurotrophic factors in the relationships between exercise dosage and neuropsychological assessments on frontal-medial-temporal lobe functions

Moderation analyses showed that exercise significantly interacted with neurotrophic factors in predicting an individual's performance in the neuropsychological assessments associated with frontal and medial temporal lobe function.

For the task measuring frontal lobe function, the model including the interaction term (BDNF × Group), which significantly predicted a higher WCST conceptual response rate ($F_{9,75} = 2.163$, $p = .036$, adjusted $R^2 = .122$) (Table 4). Both BDNF (standardized regression coefficient, *Beta* = −1.175, $p = .004$) and the interaction term, Group × BDNF (*Beta* = 1.018, $p = .010$) were significant predictors of the WCST conceptual response rate. In other words, among the exercisers, each unit increase in BDNF will decrease the WCST conceptual response rate but increase the same rate among the controls (Fig. 1).

For medial temporal function assessment, the model including the interaction term (Group × VEGF) significantly predicted the memory score in SAL ($F_{9,73} = 2.039$, $p = .049$, adjusted $R^2 = .114$). While VEGF was not a significant predictor (*Beta* = −.282, $p = .061$), Group × VEGF significantly predicted the SAL memory score (*Beta* = .813, $p = .039$). In other words, each unit increase in VEGF will result in a greater increase in the SAL memory score of the healthy controls than that of the exercisers (Fig. 2).

4. Discussion

The findings of this study indicated that regular exercise was associated with better performance on the neuropsycholo-

Table 4 Predicting cognitive functions by demographic, group condition, and neurotrophic factors; the interaction terms between group condition and neurotrophic factors are shown.

	SAL memory score		WCST conceptual response rate
Step 1 (standardized coefficient, *Beta*)		**Step 1** (standardized coefficient, *Beta*)	
Age	−.157	Age	−.376*
Sex	.089	Sex	−.018
Intellectual functioning	.196	Intellectual functioning	.042
Education	.047	Education	.359*
Positive mood	−.088	Positive mood	−.227*
Negative mood	−.177	Negative mood	−.078
Step 2 (*Beta*)		**Step 2** (*Beta*)	
Group	−.282*	Group	.059
VEGF	−.726	BDNF	−1.175*
Step 3 (*Beta*)		**Step 3** (*Beta*)	
Group × VEGF	.813*	Group × BDNF	1.018**
R^2 of the final model	.223	R^2 of the final model	.228

SAL = Spatial Associate Learning Task; WCST = Wisconsin Card Sorting Test; Group = exercise or control group; BDNF = brain-derived neurotrophic factor; VEGF: vascular endothelial growth factor.
* $p < .05$.
** $p < .01$.

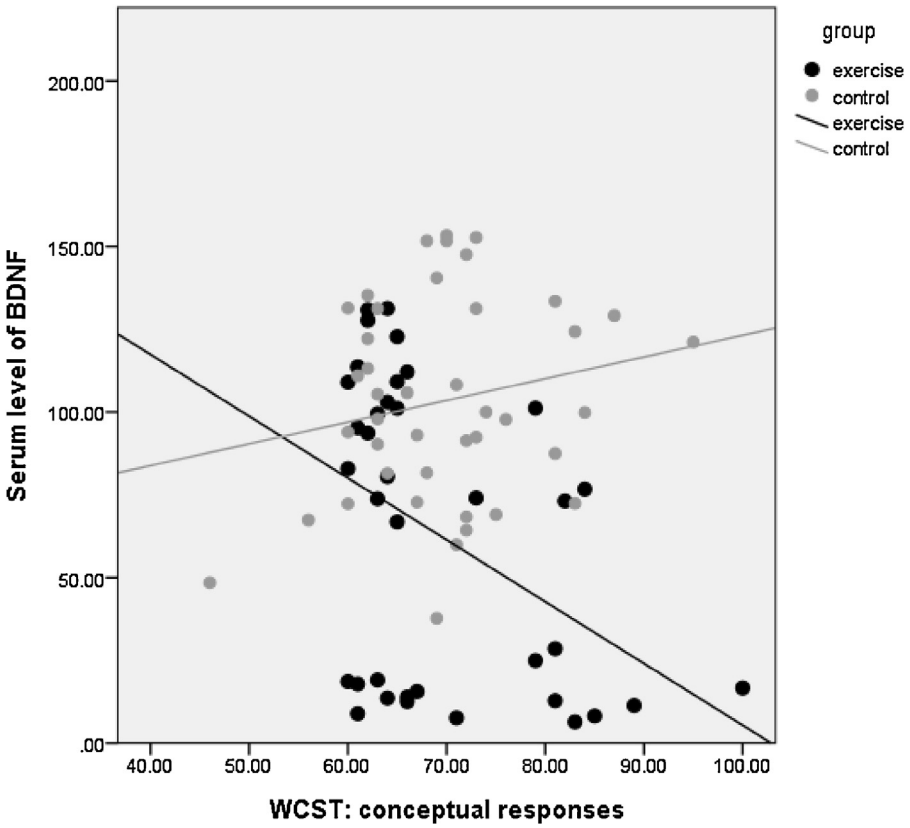

Figure 1 Scatter plots of the relationship between serum level of brain-derived Neurotrophic factor and conceptual response rate in Wisconsin Card Sorting Test in the exercise and control group. BDNF = brain-derived neurotrophic factor; WCST = Wisconsin Card Sorting Test.

gical assessment of some frontal and medial temporal lobe function. In addition, we observed a negative correlation between neurotrophic factors (BDNF and VEGF) and the neuropsychological assessments related to cognitive functions studied in the group of adolescent exercisers. Furthermore, this is the first report of an interaction between the levels of BDNF and VEGF and exercise status may predict performance in neuropsychological assessments associated with frontal and temporal lobe function.

4.1. Cognitive tasks measuring frontal and medial-temporal lobe function

Recent reviews (e.g., Guiney and Machado, 2013; Verburgh et al., 2013) have raised concerns regarding the paucity of studies that have examined the effect of regular exercise on adolescent cognitive functions, particularly, executive functions. The findings of the current study are timely and fill an important gap in the literature. This study revealed the association between chronic regular exercise and enhanced performance in the neuropsychological assessment of some frontal and medial-temporal lobe function in adolescents. Specifically, adolescent exercisers presented with improved memory, inhibitory control, and cognitive flexibility in task switching. Their superior performance remained even after controlling for their enhanced psychomotor speed compared to age-matched controls. Interestingly, the observed beneficial cognitive effects were specific to only the tests ascertaining some frontal and medial temporal lobe function. The performance on the Contrast Discrimination task, which is subserved by the occipital regions, did not reveal any group differences between the adolescent exercisers and their matched controls. Notably, we also did not observe a significant group difference on the dual task (associated with frontal lobe function) and spatial recognition tests (associated with medial-temporal function), which might be related to the power and sample size of the current study. While we see trends showing better performance in the exercise group in both tasks, we could not exclude the possibility that a larger sample size may be able to detect the statistical difference (if any). Alternative interpretations of these significant results could be (1) there are different types of functions subserved by the frontal lobe and they are not all necessarily benefited by the effects of exercise. Accordingly, our data may mean that divided attention (assessed by the dual task) may not be related to the effects of exercise. Another interpretation is that (2) recognition memory (assessed by spatial recognition test) and associative memory (assessed by spatial associative learning task) were indeed two cognitive processes which were suggested to be associated with different neural mechanisms (see Yonelinas, 1997). In this way, the current data appeared to suggest that chronic exercise would be associated with better performance in neuropsychological assessments of associative memory, but not recognition memory.

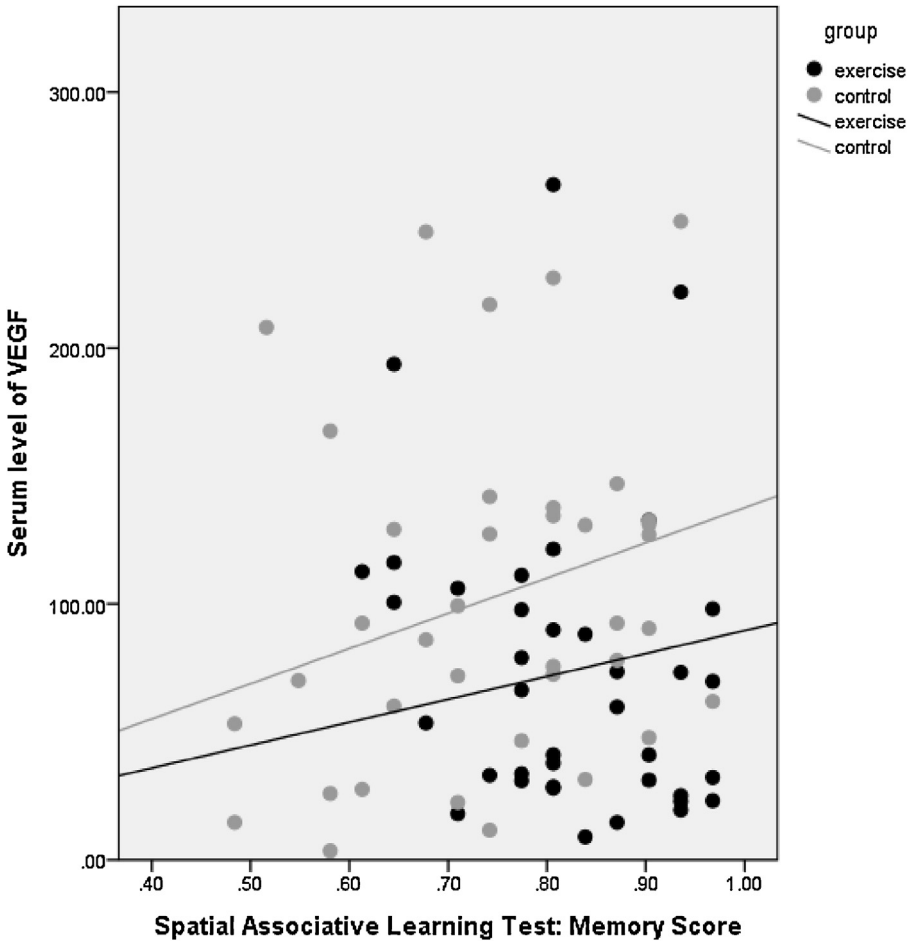

Figure 2 Scatter plots of the relationship between serum level of vascular endothelial growth factor (VEGF) and memory score in the Spatial Associative Memory Task in the exercise and control group. VEGF = vascular endothelial growth factor.

This study is one of the first human studies providing data on the relationship among exercise, cognitive functions, and neurotrophic factors in adolescents. Our data were consistent with the findings in an adolescent animal study, where exercise was associated with better performance in neuropsychological assessments, possibly through its relationship with neurotrophic factors, e.g., BDNF (Hopkins et al., 2011) and its neural effects on the hippocampus (Uysal et al., 2005). Even though the design and sample of the current study did not allow for conclusive comments on the effects of age on cognition, exercise, and neurotrophic factors, future research should further examine the relationship between exercise and cognitive functions by considering possible region-specific property as well as the influence of neurotrophic factors on this relationship.

4.2. Neurotrophic factors

Our previous animal findings (Yau et al., 2011b, 2012) adopting neurotrophic factors (BDNF and IGF-1) as outcome indicators concluded that exercise could promote neurogenesis, cell proliferation and dendritic remodeling in the medial-temporal cortex. This study extended the findings of our previous animal work to humans. Consistent with our hypothesis, there is a significant correlation between the exercise dosage and serum concentration of the neurotrophic factors studied. Interestingly, the serum concentration of the neurotrophic factors was significantly lower in the adolescent exercisers compared to their matched controls. This observation was consistent with findings in previous studies reporting that prolonged and extensive exercise training resulted in decreased neurotrophic factor levels compared to matched dormant subjects (Chan et al., 2008; Nofuji et al., 2008). However, our findings contradicted some findings of specific pre-clinical animal and human studies that reported a positive relationship between exercise and neurotrophic factor concentrations (Cotman and Engesser-Cesar, 2002; Fabel et al., 2003; Heyman et al., 2012).

The discrepant findings between this study and previous studies may relate to the chronicity and intensity of the exercise studied as well as other methodological discrepancies, e.g., timing of the measurements of the serum neurotrophic factor. For example, most studies on the acute effects of exercise on cognition measured the level of neurotrophic factors immediately after exercise, although studies examining the effects of chronic/regular exercise on cognition might measure the neurotrophic factor levels when the subjects were at rest. Thus, Cho et al. (2012) recently reported a dynamic relationship between exercise and circulating neurotrophic factors in human adults. In individuals

with high levels of cardio-respiratory fitness, the relationship between the cardio-respiratory fitness and BDNF was positive when BDNF was measured immediately after exercise, but the relationship was negative if BDNF was measured at rest. Future studies comparing the concentration of neurotrophic factors immediately after exercise and at the resting condition among regular exercisers may help to elucidate the relationship between neurotrophic factors and exercise dosage.

We observed significant associations between exercise dosage and some neurotrophic factors (BDNF and VEGF), but not IGF-1. One potential reason was that most of the extant literature that finds a positive correlation between exercise and IGF-1 made use of resistance training (e.g. Abe et al., 2005; Hameed et al., 2003), while the current study sample consisted of regular exercisers performing aerobic exercise. In fact, with a human adult sample ($n = 273$), Haydar et al. (2000) also did not find any significant correlation between aerobic exercise capacity and IGF-1.

4.3. Interaction between exercise and neurotrophic factors on cognition

Our findings have suggested that regular exercise might interact with some neurotrophic factors in influencing the performance on neuropsychological assessments associated with specific frontal and medial-temporal lobe function. To the best of our knowledge, this novel finding has never been previously reported.

For assessments related to frontal lobe function, the adolescent exercisers presented with superior cognitive flexibility, and exercise did interact with the BDNF level on cognitive flexibility. Specifically, better cognitive flexibility was predicted in the exercisers with low BDNF levels and in the sedentary controls with high BDNF levels. Furthermore, better spatial associative memory was predicted by a high level of VEGF in both the exercisers and controls, but the magnitude of the effect was dependent on the exercise habits in which the effect of VEGF on spatial associative memory in the sedentary adolescents was significantly greater than that of the exercisers. The current findings are unable to explain the mechanisms underlying these interaction effects. A previous animal study has shown that prolonged exercise might have upregulated the expression of hippocampal BDNF receptor: tropomyosin-related kinase B (TrkB), and thus increased the sensitivity of these receptors (Liu et al., 2008). Future studies may consider the phenomenon of altering receptor sensitivity and/or other neural mechanisms as possible explanation of the interaction effects observed in this study.

Previous human studies have shown that acute exercise increases the levels of neurotrophic factors in healthy sedentary participants (e.g., Hopkins et al., 2012). This finding was not replicated in this study, and we are unsure about the reason for it. As previously mentioned above, existing studies varied in the time of measurement of the serum levels of neurotrophic factors. For instance, the exercise protocol that measured the serum levels of neurotrophic factors shortly or immediately after exercise tended to observe a positive correlation (e.g., Heyman et al., 2012) while those measuring these factors when the participants were at rest did not show a similar result (e.g., Jung et al., 2011).

4.4. Limitations

Several considerations should be noted in the interpretations of the current findings. First, the sample of the current study may limit the interpretation of the effects of exercise on frontal and medial-temporal lobe function. While we selectively used neuropsychological assessments of some specific frontal and medial temporal lobe function, due to the constraint of the testing time, we fully acknowledged that there was unexplored frontal/medial-temporal lobe function which was tapped by tasks not in the current study's battery. However, the current study provides a foundation for future studies to compare and delineate the beneficial effects of exercise on different frontal and medial-temporal lobe function. There may be concerns regarding the collinearity between BDNF and VEGF. In our adolescent sample, BDNF was found to be moderately correlated with VEGF ($r = .461$, $p < .001$). This is consistent with existing literature showing a positive correlation between BDNF and VEGF in human adults. For example, Zhang et al. (2000) have recently shown that VEGF secretion could be stimulated by an increase in BDNF in human adults. While collinearity between BDNF and VEGF might exist in the current study, given that these factors were never entered as predictors in any analyses, our findings were not likely to be affected by multicollinearity.

5. Conclusions

The current study provides preliminary evidence supporting the beneficial effects of regular exercise in improving cognitive functions in the younger population. The beneficial effects were region-specific and associated with the serum levels of some neurotrophic factors. However, further studies on adolescent and the younger brains are required to delineate the effects, and the neurobiological mechanisms underpinning these effects, to create a model describing exercise and its neurobiological effects. Such a model would be extremely beneficial for guiding the use of exercise in preventative medicine to promote brain health.

Role of the funding source

This work was supported by the May Endowed Professorship and Jessie Ho Endowed Professorship of The University of Hong Kong, the Research Grant Council General Research Fund (Ref: HKU747612H and HKU745912H) and Collaborative Research Fund (PolyU9/CRF/09). The funders did not play any role in study design, data collection and analysis, decision to publish, or preparation of the article.

Conflict of interests

There is no conflict of interest with any financial organization regarding the material discussed in the article.

Acknowledgement

We would like to thank Raymond So of the Hong Kong Sports Institute for the assistance with subject recruitment and data collection.

References

Abe, T., Yasuda, T., Midorikawa, T., Sato, Y., Kearns, C.F., Inoue, K., et al., 2005. Skeletal muscle size and circulating IGF-1 are increased after two weeks of twice daily KAATSU resistance training. Int. J. Kaatsu Trianing Res. 1, 6—12.

Bechara, R.G., Kelly, Á.M., 2013. Exercise improves object recognition memory and induces BDNF expression and cell proliferation in cognitively enriched rats. Behav. Brain Res. 245, 96—100.

Baddeley, A., Sergio, D., Costanza, P., Hans, S., 1997. Dual-task performance in dysexecutive and nondysexecutive patients with a frontal lesion 11, 187—194.

Boyntona, G.M., Demba, J.B., Gloverb, G.H., Heegera, D.J., 1999. Neuronal basis of contrast discrimination. Vision Res. 39, 257—269.

Budde, H., Voelcker-Rehage, C., Pietrassyk-Kendziorra, S., Ribeiro, P., Tidow, G., 2008. Acute coordinative exercise improves attentional performance in adolescents. Neurosci. Lett. 441, 219—223.

Budde, H., Voelcker-Rehage, C., Pietrassyk-Kendziorra, S., Machado, S., Ribeiro, P., Arafat, A.M., 2010. Steroid hormones in the saliva of adolescents after different exercise intensities and their influence on working memory in a school setting. Psychoneuroendocrinology 35, 382—391.

Cao, L., Jiao, X., Zuzga, D.S., Liu, Y., Fong, D.M., Young, D., et al., 2004. VEGF links hippocampal activity with neurogenesis, learning and memory. Nat. Genet. 36, 827—835.

Cetinkaya, C., Sisman, A.R., Kiray, M., Camsari, U.M., Gencoglu, C., Baykara, B., et al., 2013. Positive effects of aerobic exercise on learning and memory functioning, which correlate with hippocampal IGF-1 increase in adolescent rats. Neurosci. Lett. 549, 177—181.

Chan, K.L., Tong, K.Y., Yip, S.P., 2008. Relationship of serum brain-derived neurotrophic factor (BDNF) and health-related lifestyle in healthy human subjects. Neurosci. Lett. 447, 124—128.

Cheng, S-T., 2004. Age and subjective well-being revisited: a discrepancy perspective. Psychol. Aging 19, 409—415.

Cho, H.-C., Kim, J., Kim, S., Son, Y.H., Lee, N., Jung, S.H., 2012. The concentrations of serum, plasma and platelet BDNF are all increased by treadmill VO_{2max} performance in healthy college man. Neurosci. Lett. 529, 78—83.

Colcombe, S., Kramer, A.F., 2003. Fitness effects on the cognitive function of older adults. Psychol. Sci. 14, 125—130.

Cotman, C.W., Engesser-Cesar, C., 2002. Exercise enhances and protects brain function. Exerc. Sport Sci. Rev. 30, 75—79.

Craig, C.L., Marshall, A.L., Sjöström, M., Bauman, A.E., Booth, M.L., Ainsworth, B.E., et al., 2003. International physical activity questionnaire: 12-country reliability and validity. Med. Sci. Sports Exerc. 35, 1381—1395.

Currie, J., Ramsbottom, R., Ludlow, H., Nevill, A., Gilder, M., 2009. Cardio-respiratory fitness, habitual physical activity and serum brain derived neurotrophic factor (BDNF) in men and women. Neurosci. Lett. 451, 152—155.

Fabel, K., Fabel, K., Tam, B., Kaufer, D., Baiker, A., Simmons, N., et al., 2003. VEGF is necessary for exercise-induced adult hippocampal neurogenesis. Eur. J. Neurosci. 18, 2803—2812.

Gu, J.-W., Gadonski, G., Wang, J., Makey, I., Adair, T.H., 2004. Exercise increases endostatin in circulation of healthy volunteers. BMC Physiol. 4, 2.

Guiney, H., Machado, L., 2013. Benefits of regular aerobic exercise for executive functioning in healthy populations. Psychon. Bull. Rev. 20, 73—86.

Hameed, M., Orrell, R.W., Cobbold, M., Goldspink, G., Harridge, S.D.R., 2003. Expression of IGF-1 splice variants in young and old human skeletal muscle after high resistance exercise. J. Phsiol. 547, 247—254.

Harris, A.J., 1958. Harris Test of Lateral Dominance: Manual of Directions. The Psychological Corporation, New York.

Haydar, Z.R., Blackman, M.R., Tobin, J.D., Wright, J.G., Fleg, J.L., 2000. The relationship between aerobic exercise capacity and circulating IGF-1 levels in healthy men and women. J. Am. Geriatr. Soc. 48, 139—145.

Heaton, R.K., Chelune, G.J., Taley, J.L., Kay, G.G., Curtis, G., 1993. Wisconsin Card Sorting Test (WCST). Manual Revised and Expanded. Psychological Assessment Resources Inc., Odessa.

Heyman, E., Gamelin, F.X., Goekint, M., Piscitelli, F., Roelands, B., Leclair, E., et al., 2012. Intense exercise increases circulating endocannabinoid and BDNF levels in humans—possible implications for reward and depression. Psychoneuroendocrinology 37, 844—851.

Hopkins, M.E., Davis, F.C., Vantieghem, M.R., Whalen, P.J., Bucci, D.J., 2012. Differential effects of acute and regular physical exercise on cognition and affect. Neuroscience 215, 59—68.

Hopkins, M.E., Nitecki, R., Bucci, D.J., 2011. Physical exercise during adolescence versus adulthood: differential effects on object recognition memory and BDNF levels. Neuroscience 194, 84—94.

Howard, M.W., Mrigankka, Fotedar, M.S., Datey, A.V., Hasselmo, M.E., 2005. The temporal context model in spatial navigation and relational learning: toward a common explanation of medial temporal lobe function across domains. Psychol. Rev. 112, 75—116.

IPAQ Research Committee, 2005. International Physical Activity Questionnaire (IPAQ) scoring protocol. , Available from.http://www.ipaq.ki.se/scoring.pdf (accessed 01.05.13).

Jung, S., Kim, J., Davis, J., Blair, S., Cho, H.-C., 2011. Association among basal serum BDNF, cardiorespiratory fitness and cardiovascular disease risk factors in untrained healthy Korean men. Eur. J. Appl. Physiol. 111, 303—311.

Kobilo, T., Liu, Q-R., Gandhi, K., Mughal, M., Shaham, Y., van Praag, H., 2011. Running is the neurogenic and neurotrophic stimulus in environmental enrichment. Learn. Mem. 18, 605—609.

Kraus, R.M., Stallings, H.W., Yeager, R.C., Gavin, T.P., 2004. Circulating plasma VEGF response to exercise in sedentary and endurance-trained men. J. Appl. Physiol. 96, 1445—1450.

Larson, E.B., Wang, L., Bowen, J.D., McCormick, W.C., Teri, L., Crane, P., et al., 2006. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann. Intern. Med. 144, 73—81.

Lau, B.W-M., Yau, S-Y., Lee, T.M.C., Ching, Y-P., Tang, S-W., So, K-F., 2011. Effect of corticosterone and paroxetine on masculine mating behavior: possible involvement of neurogenesis. J. Sex. Med. 8, 1390—1403.

Lee, T.M.C., Chan, C.C.H., 2000. Stroop interference in Chinese and English. J. Clin. Exp. Neuropsychol. 22, 465—471.

Liu, Y-F., Chen, H-I., Yu, L., Kuo, Y-M., Wu, F-S., Chuang, J-I., et al., 2008. Upregulation of hippocampal TrkB and synaptotagmin is involved in treadmill exercise-enhanced aversive memory in mice. Neurobiol. Learn. Mem. 90, 81—89.

Nofuji, Y., Suwa, M., Moriyama, Y., Nakano, H., Ichimiya, A., Nishichi, R., et al., 2008. Decreased serum brain-derived neurotrophic factor in trained men. Neurosci. Lett. 437, 29—32.

Pereira, A.C., Huddleston, D.E., Brickman, A.M., Sosunov, A.A., Hen, R., McKhann, G.M., et al., 2007. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc. Natl. Acad. Sci. U.S.A. 104, 5638—5643.

Qu, N.N., Li, K.J., 2004. Study on the reliability and validity of international physical activity questionnaire (Chinese Version IPAQ). Chin. J. Epidemiol. 25, 265—268.

Raven, J., Raven, J.C., Court, J.H., 2000. Standard Progressive Matrices. Psychology Press, Oxford.

Reitan, R.M., Wolfson, D., 1985. The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation. Neuropsychology Press, Tucson, AZ.

Schwarz, A.J., Brasel, J.A., Hintz, R.L., Mohan, S., Cooper, D.M., 1996. Acute effect of brief low- and high-intensity exercise on circulating insulin-like growth factor (IGF) I, II, and IGF-binding

protein-3 and its proteolysis in young healthy men. J. Clin. Endocrinol. Metab. 81, 3492—3497.

Smith, P.J., Blumenthal, J.A., Hoffman, B.M., Cooper, H., Strauman, T.A., Welsh-Bohmer, K., et al., 2010. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosom. Med. 72, 239—252.

Stroth, S., Kubesch, S., Dieterle, K., Ruchsow, M., Heim, R., Kiefer, M., 2009. Physical fitness, but not acute exercise modulates event-related potential indices for executive control in healthy adolescents. Brain Res. 1269, 114—124.

Stuss, D.T., Floden, D., Alexander, M.P., Levine, B., Katz, D., 2001. Stroop performance in focal lesion patients: dissociation of processes and frontal lobe lesion location. Neuropsychologia 39, 771—786.

Stuss, D.T., Levine, B., Alexander, M.P., Hong, J., Palumbo, C., Hamer, L., Murphy, M.J., Izukawa, D., 2000. Wisconsin Card Sorting Test performance in patients with focal frontal and posterior brain damage: effects of lesion location and test structure on separable cognitive processes. Neuropsychologia 38, 388—402.

Trejo, J.L., Carro, E., Torres-Alemán, I., 2001. Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. J. Neurosci. 21, 1628—1634.

Trivedi, M.H., Greer, T.L., Church, T.S., Carmody, T.J., Gannemann, B.D., Galper, D.I., et al., 2011. Exercise as an augmentation treatment for nonremitted major depressive disorder: a randomized, parallel dose comparison. J. Clin. Psychiatry 72, 677—684.

Uysal, N., Tugyan, K., Kayatekin, B.M., Acikgoz, O., Bagritanik, H.A., Gonenc, S., et al., 2005. The effects of regular aerobic exercise in adolescent period on hippocampal neuron density, apoptosis and spatial memory. Neurosci. Lett. 383, 241—245.

van Praag, H., 2009. Exercise and the brain: something to chew on. Trends Neurosci. 32, 283—290.

van Praag, H., Kempermann, G., Gage, F.H., 1999. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat. Neurosci. 2, 266—270.

Vaynman, S., Ying, Z., Gomez-Pinilla, F., 2004. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. Eur. J. Neurosci. 20, 2580—2590.

Verburgh, L., Königs, M., Scherder, E.J.A., Oosterlaan, J., 2013. Physical exercise and executive functions in preadolescent children, adolescents and young adults: a meta-analysis. Br. J. Sports. Med. (Epub ahead of print).

Voss, M.W., Nagamatsu, L.S., Liu-Ambrose, T., Kramer, A.F., 2011. Exercise, brain, and cognition across the lifespan. J. Appl. Physiol. 111, 1505—1513.

Walker, K.S., Kambadur, R., Sharma, M., Smith, H.K., 2004. Resistance training alters plasma myostatin but not IGF-1 in healthy men. Med. Sci. Sports Exerc. 36, 787—793.

Yarrow, J.F., White, L.J., McCoy, S.C., Borst, S.E., 2010. Training augments resistance exercise induced elevation of circulating brain derived neurotrophic factor (BDNF). Neurosci. Lett. 479, 161—165.

Yau, S-Y., Lau, B.W-M., So, K-F., 2011a. Adult hippocampal neurogenesis: a possible way how physical exercise counteracts stress. Cell Transplant. 20, 99—111.

Yau, S.-Y., Lau, B.W-M., Tong, J.-B., Wong, R., Ching, Y.-P., Qiu, G., et al., 2011b. Hippocampal neurogenesis and dendritic plasticity support running-improved spatial learning and depression-like behaviour in stressed rats. PLOS ONE 6, e24263.

Yau, S.-Y., Lau, B.W-M., Zhang, E.-D., Lee, J.C., Li, A., Lee, T.M.C., et al., 2012. Effects of voluntary running on plasma levels of neurotrophins, hippocampal cell proliferation and learning and memory in stressed rats. Neuroscience 222, 289—301.

Yonelinas, A.P., 1997. Recognition memory ROCs for item and associative information: The contribution of recollection and familiarity. Mem. Cognit. 25, 747—763.

Zhang, L., Hu, Y., Sun, C-Y., Li, J., Guo, T., Huang, J., Chu, Z-B., 2000. Lentiviral shRNA silencing of BDNF inhibits *in vivo* multiple myeloma growth and angiogenesis via down-regulated stroma-derived VEGF expression in the bone marrow milieu. Cancer Sci. 101, 1117—1124.