

Acute moderate exercise enhances compensatory brain activation in older adults

Kazuki Hyodo^a, Ippeita Dan^b, Kazuya Suwabe^a, Yasushi Kyutoku^b, Yuhki Yamada^a, Mitsuya Akahori^a, Kyeongho Byun^a, Morimasa Kato^c, Hideaki Soya^{a,*}

^a Laboratory of Exercise Biochemistry and Neuroendocrinology, Institute for Health and Sports Sciences, University of Tsukuba, Tsukuba, Japan

^b Center for Development of Advanced Medical Technology, Jichi Medical University, Tochigi, Japan

^c Department of Health and Nutrition, Yamagata Prefectural Yonezawa Women's Junior College, Yonezawa, Japan

Received 20 September 2011; received in revised form 15 December 2011; accepted 19 December 2011

Abstract

A growing number of reports state that regular exercise enhances brain function in older adults. Recently a functional near-infrared spectroscopy (fNIRS) study revealed that an acute bout of moderate exercise enhanced activation of the left dorsolateral prefrontal cortex (L-DLPFC) associated with Stroop interference in young adults. Whether this acute effect is also applicable to older adults was examined. Sixteen older adults performed a color-word matching Stroop task before and after 10 minutes of exercise on a cycle ergometer at a moderate intensity. Cortical hemodynamics of the prefrontal area was monitored with a fNIRS during the Stroop task. We analyzed Stroop interference (incongruent-neutral) as Stroop performance. Though activation for Stroop interference was found in the bilateral prefrontal area before the acute bout of exercise, activation of the right frontopolar area (R-FPA) was enhanced after exercise. In the majority of participants, this coincided with improved performance reflected in Stroop interference results. Thus, an acute bout of moderate exercise improved Stroop performance in older adults, and this was associated with contralateral compensatory activation.

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Keywords: Normal aging; Executive function; Stroop task; Prefrontal cortex; Compensation; Frontopolar area; Functional near infrared spectroscopy; Optical topography; Moderate exercise

1. Introduction

Normal aging entails cognitive deterioration represented as declines in processing speed, working memory, inhibitory function, and long-term memory (Park et al., 2002). Among these, age-related inhibitory dysfunction is considered to cause attentional dysregulation, which further affects age-associated deficits in various cognitive functions (Hasher and Zacks, 1988).

The neural substrate for age-related inhibitory dysfunction may be observed through functional imaging during the

Stroop task (Stroop, 1935), a typical task for measuring inhibitory function. In the traditional Stroop paradigm employing the matching of color and word, color-words printed in different foreground colors are presented to observers. Then, the observers are required to name the color of the color-word irrespective of its meaning. Because of the automatic nature of word reading, cognitive control is required for directing attention to the color identification process. Consequently, behavioral performance, most often measured as reaction time, is impaired in the incongruent condition (e.g., the word “red” in blue letters) as compared with the neutral condition (e.g., the letters “××××” in blue letters) and the congruent condition (e.g., the word “blue” in blue letters) (Cohen et al., 1990). During the incongruent condition, the 2 conflicting sources of color information cause a competing effect known as Stroop interference,

* Corresponding author at: Laboratory of Exercise Biochemistry and Neuroendocrinology, Institute for Health and Sports Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba 305-8574, Japan. Tel.: +81 29 853 2620; fax: +81 29 853 2620.

E-mail address: hsoya@taiiku.tsukuba.ac.jp (H. Soya).

which is most typically observed as a prolonged reaction time compared with the neutral or congruent conditions (Laird et al., 2005). With increasing age, Stroop task performance usually declines, and this entails an increase of the Stroop interference effect (See and Ryan, 1995).

The neural substrate underlying the age-associated Stroop task performance change has been revealed by neuroimaging studies using functional magnetic resonance imaging (fMRI). While the anterior cingulate cortex (ACC) and left lateral prefrontal cortex (LPFC) have been typically recruited in younger adults (MacDonald et al., 2000), activation of the bilateral prefrontal cortex (PFC) has often been observed in older adults (Langenecker et al., 2004; Zysset et al., 2006). Such age-related changes of prefrontal activation have been conceptualized as a model called hemispheric asymmetry reduction in older adults (HAROLD), stating that given similar conditions, there is less lateralized prefrontal activation in older adults than in younger adults during cognitive performance (Cabeza, 2002). One major interpretation for the age-related lateralization reduction and overrecruitment seen in the HAROLD model is the compensatory hypothesis (Cabeza, 2002). It states that older adults recruit more areas of the contralateral hemisphere than younger adults to achieve or attempt to achieve the same levels of performance. A wealth of evidence suggests that additional contralateral recruitment reflects functional compensation in cognitive functions including episodic memory, working memory, and visual attention (Cabeza et al., 2004; Reuter-Lorenz et al., 2000; Rosen et al., 2002).

On the other hand, the cognitive functions of older adults may be altered by intervention, including exercise. A growing number of animal and human studies have revealed that exercise enhances brain function and may lead to the recovery of cognitive functions. Animal studies have revealed that exercise induces the upregulation of neurogenesis and synaptic plasticity in the hippocampus (van Praag et al., 1999, 2005). Human neuroimaging studies have reported that aerobic intervention leads to increased gray and white matter volume and enhanced cognitive functions (Colcombe et al., 2004, 2006). Among them, executive functions, which include inhibition, working memory, and cognitive flexibility, have been known to be positively affected by exercise (Colcombe and Kramer, 2003).

While the majority of studies have investigated the chronic effects of exercise, a growing number of studies have also reported beneficial influences of acute exercise on cognitive function across a life span (Hillman et al., 2009; Kamijo et al., 2009). Particularly, moderate intensity exercise is found effective in improving cognitive performance in various neuropsychological tests, including choice reaction time tasks (Chmura et al., 1994), decision-making tasks (McMorris et al., 1999), and inhibitory control tasks (Kamijo et al., 2004, 2007). In conjunction with the examination of the cognitive effects of acute exercise, the search for their neural substrates has been performed mainly in the

domain of event-related potential (ERP) research. Because P300 (or P3) is believed to represent the brain activity required to maintain working memory when the mental model of the stimulus environment is updated (Donchin and Coles, 1988), it is regarded as an appropriate neural substrate for improved cognitive performance. Several studies have reported increased amplitude and shortened latency of P300 components in relation to the performance improvements caused by an acute bout of exercise (Hillman et al., 2003; Kamijo et al., 2007; Magnié et al., 2000). While ERP provides considerable temporal information about cortical functions, it provides only rough information regarding where in the brain the effect originated.

As a promising neuroimaging technique to resolve this ERP localization problem, Yanagisawa et al. (2010) recently introduced functional near-infrared spectroscopy (fNIRS) for investigating the acute effects of exercise on cognition. fNIRS is an optical method that noninvasively monitors the cerebral hemodynamics of oxygenated- and deoxygenated hemoglobin species (oxy-Hb and deoxy-Hb, respectively) by measuring changes in the attenuation of near infrared light passing through tissue (Koizumi et al., 2003; Obrig and Villringer, 2003). Unlike other neuroimaging methods, fNIRS is compact, portable, and can be easily installed in a gym (Timinkul et al., 2008). These features allow strict control of exercise intensity using gym facilities, and subsequent on-site neuroimaging allows precise control of the interval between exercise and neuroimaging experiments. In addition, fNIRS allows subjects to perform tasks in a natural and comfortable environment without being confined to a small, restricted space, keeping possible outside influences on cognitive tasks minimal.

Using fNIRS, Yanagisawa et al. (2010) found that younger adults dominantly recruited the left LPFC during Stroop tasks, and that an acute bout of moderate exercise induced increased activation of the left dorsolateral prefrontal cortex (DLPFC) due to Stroop interference. The increased activation coincided with improved cognitive performance in the majority of participants. These results could be interpreted as exercise enhancing the cortical function of a task-specific region, leading to improved cognitive performance.

In extending these findings to older adults, 2 further research questions arose. One is whether the acute effect of exercise on cognition observed in younger adults also occurs in older adults. The other is, if so, whether the increased cognitive performance is associated with task-specific left DLPFC activation or contralateral compensatory response. Because some fNIRS studies have successfully reported HAROLD during cognitive tasks (Herrmann et al., 2006; Tsujii et al., 2010), fNIRS would facilitate a detailed examination on how HAROLD and exercise-induced cognitive reinforcement interact in older adults.

Thus, in this study, we aimed to examine where in the LPFC activation related to Stroop interference changes due

to an acute bout of moderate exercise in older adults. Given the chronic and acute effects of moderate exercise, enhancing executive function in older adults, it is expected that an acute bout of moderate exercise can also induce a rapid enhancement of Stroop performance in them. We first examined whether the acute exercise-induced cognitive improvement that we observed in younger adults is also applicable to older adults. Then, we explored the neural substrate for the acute cognitive improvement in older adults, namely, whether it was in the task-specific region or whether it reflected compensatory functions.

2. Methods

2.1. Subjects

Thirty-three healthy older adults (5 females) participated in the study. Their cognitive and physical abilities varied greatly. Because this study was intended to assess the effects of an acute bout of exercise on cognitively active older adults with the ability to perform moderate exercise, the following criteria were applied. First, to exclude participants with possible cognitive decline, those with a Stroop task correct answer rate of less than 80% were excluded (3). Second, those who found it difficult to exercise at a moderate intensity for 10 minutes continuously were excluded (4). In addition, those with unintentional false reports in their medical biography (high blood pressure or type II diabetes) (8), those who fell asleep during cognitive tasks (1), and those with noisy fNIRS data (1), were excluded. Thus, the remaining 16 subjects were analyzed: 3 females; mean age 69.3 ± 3.5 years (range 64–74 years), body mass 60.8 ± 4.6 kg, height 164 ± 8.6 cm. Neither Geriatric Depression Scale (GDS) nor Mini Mental State Examination (MMSE) found any abnormalities (GDS: 0.8 ± 1.6 [range 0–5], MMSE: 28.8 ± 1.6 [range 27–30]). Subjects had normal or corrected-to-normal vision, normal color vision, and were native Japanese speakers. None had a history of neurological, major medical, or psychiatric disorders, and none were taking medication at the time of measurement. Written informed consent was obtained from all subjects prior to participation. This study was approved by the institutional Ethics Committee of Tsukuba University, and the protocol was in accordance with the Declaration of Helsinki guidelines.

2.2. Experimental procedure

The subjects underwent 2 fNIRS conditions, exercise (EX) and control (CTL), each with 2 sessions (Fig. 1A). In the EX condition, subjects performed the Stroop task before (pre-session) and 15 minutes after (post-session) an acute bout of moderate exercise. Because we revealed in a pilot study that middle cerebral artery mean blood velocity (MCA V_{mean}) and skin blood flow (SBF) increase with 10 minutes of exercise at a moderate intensity and return to rest levels within 15 minutes, we set 15 minutes as the time

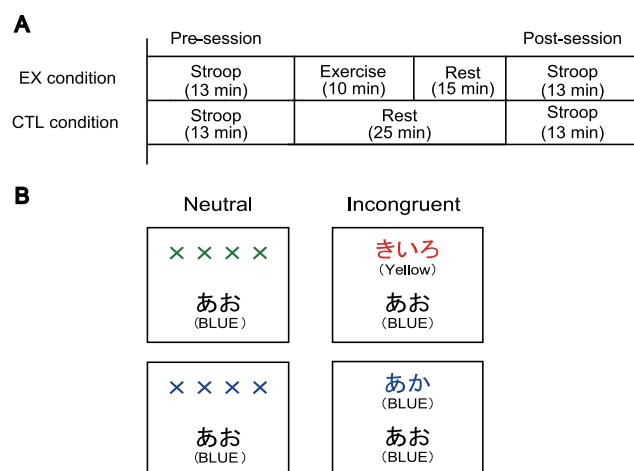


Fig. 1. Experimental design. (A) Procedures of exercise (EX) and control (CTL) conditions. Cortical hemodynamics was monitored with functional near-infrared spectroscopy (fNIRS) while subjects performed the Stroop task. (B) Stroop task presentation. Examples of single trials for the neutral and incongruent conditions of the color-word matching Stroop task are depicted. Stimuli were presented in Japanese. The English translations are indicated in parentheses.

between the end of exercise and the postsession Stroop task to eliminate possible contamination by exercise-induced physiological noise and to clearly detect task-induced cortical hemodynamics (Yanagisawa et al., 2010). In the CTL condition, subjects rested during the interval between pre- and postsessions instead of performing exercise. Cortical hemodynamics was monitored with fNIRS while subjects performed the Stroop task. The 2 conditions were implemented using a crossover design, and the order was counterbalanced across subjects.

2.3. Graded exercise test

Prior to the experiment, the subjects underwent a graded exercise test using a recumbent ergometer (Strength-ergo 240, Mitsubishi Electric Corporation, Tokyo, Japan) to determine their ventilatory threshold (VT) (Beaver et al., 1986). The exercise intensity at VT corresponds to approximately 50% of maximal oxygen uptake ($\dot{V}O_{2\text{max}}$) (Beaver et al., 1986). This has proven applicable to older adults (Thomas et al., 1985). Because VT can be accurately measured, we adopted it to serve as a reproducible and objective measure to define exercise intensity. According to the guidelines of the American College of Sports Medicine (ACSM) (2010), “moderate exercise is defined as exercise with an intensity of approximately 40% to 59% $\dot{V}O_{2\text{max}}$ ”. Therefore, exercise intensity at VT can be considered to well represent moderate exercise. Another objective measure would be $\dot{V}O_{2\text{max}}$ itself. However, we selected VT rather than $\dot{V}O_{2\text{max}}$ for the following 2 reasons: first, VT has proven to be a more critical determinant for evaluating submaximal exercise capacity than is $\dot{V}O_{2\text{max}}$ (Weltman et al., 1978); second, raising exercise intensity to the level of

$\dot{V}O_{2\max}$ was considered risky for older adults and avoided for medical considerations.

After a warm-up exercise of 3 minutes at 5 W, the power was increased incrementally by 1 W every 6 seconds. The heart rate (HR) and the subject's rating of perceived exertion (RPE) (Borg, 1970) were recorded every minute. In order to reach VT while minimizing the burden on subjects for safety reasons, we set the exercise to last until the RPE reached 17 (very hard). The pedaling rate was kept at 50 rpm.

Ventilation parameters, oxygen intake ($\dot{V}O_2$), and carbon dioxide output ($\dot{V}CO_2$) were measured breath-by-breath by an aeromonitor (Aeromonitor AE280S, Minato Medical Science, Osaka, Japan) at a sampling rate of 0.1 Hz, according to Harms et al. (1998). VT was determined with v-slope methods using the aeromonitor according to Itoh et al. (2005). Briefly, respiratory gas measures were graphically plotted, and VT was the point at which carbon dioxide output increase changed from linear to nonlinear.

2.4. Psychophysical procedures

We adopted the color-word matching Stroop task (Schroeter et al., 2003; Stroop, 1935; Yanagisawa et al., 2010) in an event-related design (Fig. 1B). We presented 2 rows of letters on a computer screen, and instructed the subjects to decide whether the color of the letters in the top row corresponded to the color name printed in the bottom row. The subjects were to input their choice by pressing a button with their forefingers to give “yes” or “no” responses. The left-right order of the 2 buttons was counter-balanced across subjects. Correct answer rate and reaction time were also measured. For neutral trials, the top row contained groups of X's (XXXX) printed in red, green, blue, or yellow, and the bottom row contained the words “RED”, “GREEN”, “BLUE”, or “YELLOW” printed in black. For incongruent trials, the top row contained the words “RED”, “GREEN”, “BLUE”, or “YELLOW” printed in an incongruent color. All the word stimuli were presented in Japanese. The top row was presented 350 ms before the lower row to achieve sequential visual attention. The correct answer rate assigned to yes and no was 50% each. Each experimental session consisted of 60 trials including 30 neutral and 30 incongruent trials presented in random order. Each trial was separated by an interstimulus interval showing a fixation cross for 9–13 seconds to avoid prediction of the timing of the subsequent trial. The stimulus remained on the screen until the response was given, or for 2 seconds. Prior to the experiment, a practice session consisting of 3 trials was performed.

2.5. fNIRS instruments

We used the multichannel fNIRS optical topography system (ETG-7000, Hitachi Medical Corporation, Kashiwa, Japan) set with 2 wavelengths of near-infrared light (785 and 830 nm). We analyzed the optical data based on the

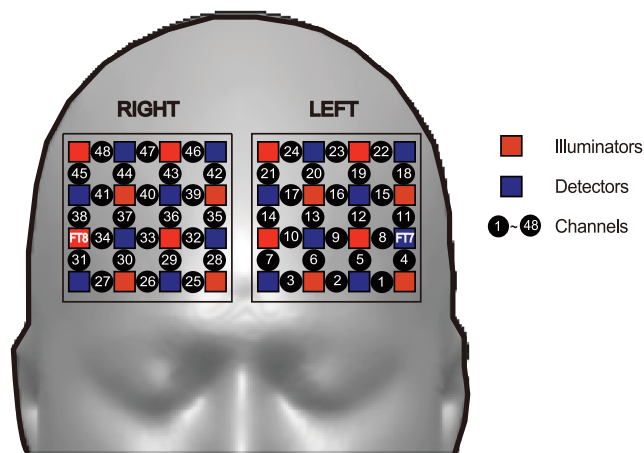


Fig. 2. Schematic representation of functional near-infrared spectroscopy (fNIRS) probes. Red squares show illuminators and blue squares show detectors. Channels are presented as circles with channel numbers. FT7 and FT8 indicate the international 10-10 standard positions.

modified Beer-Lambert Law (Cope et al., 1988) as previously described (Maki et al., 1995). This method allowed us to calculate signals reflecting the oxygenated hemoglobin (oxy-Hb), deoxygenated hemoglobin (deoxy-Hb), and total hemoglobin (total-Hb) concentration changes, calculated in units of millimolar-millimeter (mM-mm) (Maki et al., 1995). We analyzed oxy-Hb and deoxy-Hb signals. The sampling rate was set at 10 Hz.

2.6. fNIRS probe placement

We set the fNIRS probes to cover the LPFC activation foci as in previous studies (e.g., Yanagisawa et al., 2010) (Fig. 2). We used 2 sets of 4×4 multichannel probe holders, consisting of 8 illuminating and 8 detecting probes arranged alternately at an interprobe distance of 3 cm, resulting in 24 channels (CH) per set. The left probe holder was placed such that probe 5 (between CH 4 and CH 11) was placed over FT7, with the medial edge of the probe column being parallel to the medial line. Likewise, the right probe holder was placed symmetrically.

2.7. Virtual registration of fNIRS channels to MNI space

We employed virtual registration (Tsuzuki et al., 2007) to register fNIRS data to Montreal Neurological Institute (MNI) standard brain space (Brett et al., 2002). Briefly, this method allows us to place a virtual probe holder on the scalp by simulating the holder's deformation and by registering probes and channels onto reference brains in our magnetic resonance image (MRI) database (Okamoto and Dan, 2005; Okamoto et al., 2004). We performed a statistical analysis of the MNI coordinate values for the fNIRS channels to obtain the most likely estimate of the location of given channels for the group of subjects, and the spatial variability associated with the estimation (Singh et al., 2005). Finally, we anatomically labeled the estimated locations using a

Matlab function that reads anatomical labeling information coded in a macroanatomical brain atlas (Shattuck et al., 2008).

2.8. Analysis of near-infrared spectroscopy data

Individual timeline data for the oxy- and deoxy-Hb signal of each channel were preprocessed with a bandpass filter using cutoff frequencies of 0.04 Hz to remove baseline drift and 0.7 Hz to filter out heartbeat pulsations. From the preprocessed time series data, we obtained channel-wise and subject-wise contrasts by calculating the intertrial mean of differences between the oxy- and deoxy-Hb signals of peak (6–8 seconds after trial onset for oxy-Hb and 7–9 seconds after trial onset for deoxy-Hb) and baseline (0–2 seconds before trial onset) periods. The contrasts obtained were subjected to second level, random effects group analysis. Statistical analyses were performed using SPSS Statistical Packages version 19 (SPSS, Inc., Chicago, IL, USA). The specific flow of statistical analyses is described in 3. Results.

There are several notes on statistical procedures. We performed statistical analyses on regions of interest (ROIs). As per a previous study, we classified activated channels into 6 ROIs (Yanagisawa et al., 2010). We combined 3 or 4 neighboring channels based on a widely used anatomical labeling system, LBPA40 (Shattuck et al., 2008), to form each ROI.

The regions included the left dorsolateral PFC (L-DLPFC; channels 13, 14, 16, and 17), left ventrolateral PFC (L-VLPFC; channels 2, 6, and 9), left frontopolar area (L-FPA; channels 3, 7, and 10), right dorsolateral PFC (R-DLPFC; channels 35, 36, 39, and 40), right ventrolateral PFC (R-VLPFC; channels 26, 29, and 33), and right frontopolar area (R-FPA; channels 25, 28, and 32) (Fig. 2). This procedure is considered valid because optical properties of neighboring channels are known to be similar (Katagiri et al., 2010). However, setting ROIs as a factor in analysis of variance (ANOVA) should be avoided because their optical properties are known to vary systematically, causing bias in the statistical analyses. Thus, we limited our statistical analyses to ROI-wise. For controlling family-wise errors, we used the Holm method (Holm, 1979).

3. Results

3.1. Verification of moderate exercise intensity

In the EX condition, we evaluated whether subjects could perform exercise at a moderate intensity for 10 minutes by monitoring HR and RPE every minute. At the end of the exercise, HR and RPE were 106.8 ± 11.0 (beats per minute) and 12.5 ± 1.0 (points), which, as per the guidelines of the ACSM (American College of Sports Medicine, 2010), are in the range of moderate exercise intensity.

3.2. Behavioral results

We first examined whether a general tendency in the Stroop task could be reproduced in all the conditions used in this experiment. Reaction time (RT) and error rate were subjected to a repeated measures 3-way ANOVA with task (incongruent/neutral), exercise (EX/CTL), and session (pre/post) being within-subject factors. Because the purpose of the ANOVA was to examine occurrences of the Stroop effect, we limited the range of our analysis to the main effect of task. The ANOVA for RT and error rate exhibited significant main effects of task ($F(1,15) = 592.85$, $p < 0.001$, Fig. 3A, and $F(1,15) = 22.65$, $p < 0.001$, Fig. 3B, respectively). These results verified that Stroop interference could be generally observed in all the conditions used in this study (Table 1).

To clarify the effect of an acute bout of moderate exercise on a specifically defined cognitive process, we focused on the analyses of Stroop interference. The (incongruent – neutral) contrast that is assumed to represent Stroop interference was calculated and subjected to repeated measures of 2-way ANOVA with exercise (EX/CTL) and session (pre/post) being within-subject factors. The ANOVA for RT exhibited a significant interaction between exercise and session factors ($F(1,15) = 5.77$, $p < 0.05$) (Fig. 3C). On the other hand, there was no significant interaction or main effect for error rate.

Next, to examine the interaction, we calculated the difference of the degree of Stroop interference between post- and pre-sessions: ([incongruent – neutral] of pre-session – [incongruent – neutral] of post-session) contrast for both the EX and CTL groups, separately, and compared the difference between them. The RT difference was significantly more negative in the EX condition than in the CTL condition ($t(15) = -2.42$, $p < 0.05$, paired t test) (Fig. 3D). This result demonstrates that, in older adults, an acute bout of moderate exercise causes significant improvement in cognitive performance reflected in Stroop interference as measured by RT.

3.3. fNIRS results

First, we sought the cortical regions associated with Stroop interference. Among the 4 conditions used in the current study, pre-EX and pre-CTL conditions are free from any effects of exercise or prolonged rest periods. Therefore, we averaged the (incongruent – neutral) contrasts for these 2 conditions for each subject before the group analyses, and performed a ROI-wise analysis. For oxy-Hb, significant Stroop interference (i.e., incongruent > neutral) was found in all ROIs (1-sample t test, $p < 0.05$, Holm-corrected) (Holm, 1979) (Fig. 4). For deoxy-Hb, significant Stroop interference was found only in the bilateral DLPFC (1-sample t test, $p < 0.05$, Holm-corrected) (Holm, 1979). The time lines of oxy-Hb and

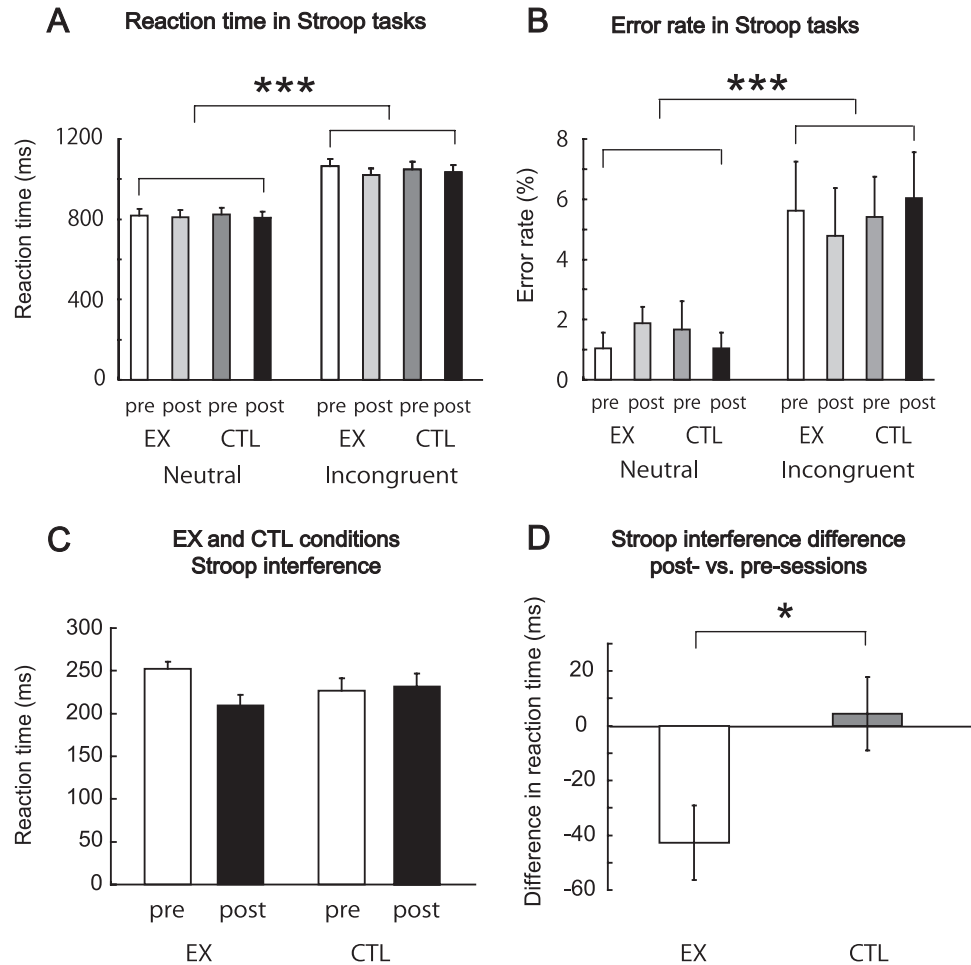


Fig. 3. Stroop task performance. (A) Comparisons between incongruent and neutral conditions for reaction time (RT). Incongruent condition exhibited significantly slower reaction time ($*** p < 0.001$). (B) Comparisons between incongruent and neutral conditions for error rate. Significant Stroop interference effects can be observed ($*** p < 0.001$). (C) The mean difference of reaction times in incongruent and neutral conditions indicating the Stroop interference for each condition. (D) Stroop interference differences between post- and pre-sessions in reaction time for each condition. RT differences are significantly greater in the exercise (EX) condition than in the control (CTL) condition ($* p < 0.05$). Error bars indicate standard errors.

deoxy-Hb during the Stroop task for all ROIs are shown in [Supplementary Fig. 1](#).

We assessed the effect of an acute bout of moderate exercise on Stroop interference. The (incongruent – neutral) contrasts were analyzed with a repeated measures 2-way

ANOVA including exercise (EX/CTL) and session (pre/post) as within-subject factors. In this design, the effect of an acute bout of moderate exercise on Stroop interference was expected to appear as an interaction between the 2 factors because pre-EX and pre-CTL were identical. For

Table 1
Stroop task performance

	Reaction time		Error rate	
	Pre	Post	Pre	Post
EX condition				
Neutral	819.4 ± 32.6	810.8 ± 36.1	1.0 ± 2.0	1.9 ± 5.1
Incongruent	1071.9 ± 36.1	1020.5 ± 34.4	5.4 ± 5.1	6.0 ± 5.9
CTL condition				
Neutral	825.2 ± 35.7	808.0 ± 30.9	1.7 ± 3.7	1.0 ± 2.0
Incongruent	1052.1 ± 40.6	1039.3 ± 36.4	5.6 ± 6.3	4.8 ± 6.1

Intersubject mean and standard error of reaction times (ms) and error rates (%) are shown for each session of each condition (mean ± standard error of the mean).

Key: CTL, control; EX, exercise.

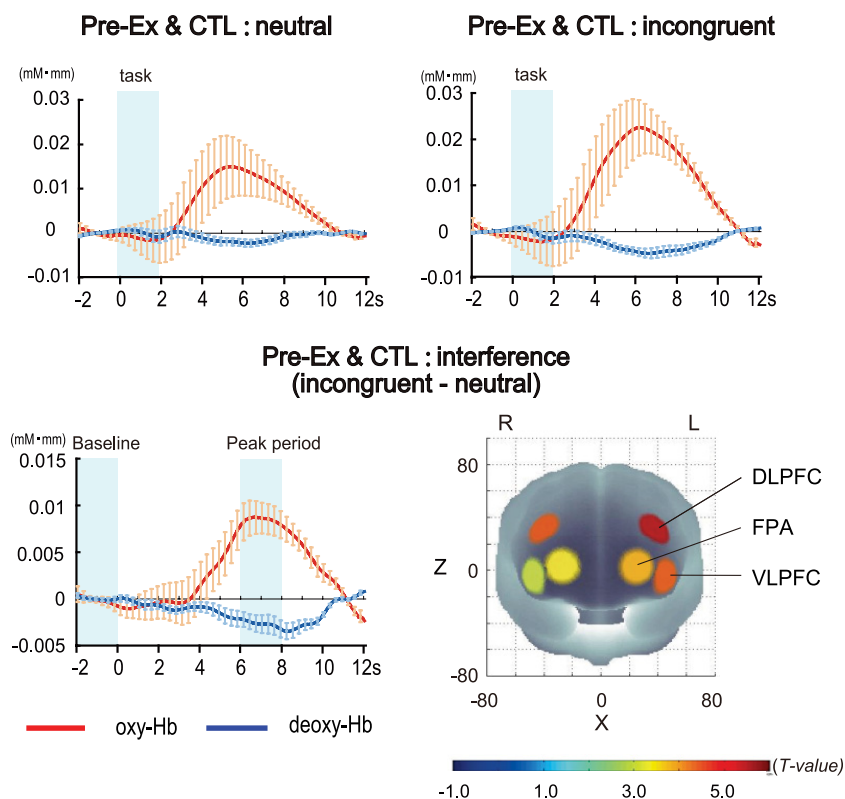


Fig. 4. Cortical activation patterns during the Stroop task for preessions in the exercise condition (pre-EX) and in the control condition (pre-CTL). Presented data are based on averaged data between pre-EX and pre-CTL sessions. The 2 graphs in the upper row and the bottom left graph show the timelines for oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) signals from a representative region of interest (ROI) (left dorsolateral prefrontal cortex [L-DLPFC]). Error bars indicate standard errors at given time points. Each time line is adjusted to the average value of the baseline period (set as 0). Oxy-Hb and deoxy-Hb signals are shown in arbitrary units (mM·mm). Periods of peak cortical activation for oxy-Hb (6–8 seconds after the task onset) and baseline (2–0 seconds before the task onset) are shown for the Stroop-interference condition. The bottom right figure is a t-map of oxy-Hb signal change reflecting the Stroop interference effect (incongruent – neutral). *T*-values are shown according to the color bar. All 6 ROIs, bilateral dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and frontopolar area (FPA) exhibit significant Stroop interference ($p < 0.05$, Holm-corrected).

oxy-Hb, the ANOVA performed on each of the 6 ROIs revealed significant interaction between the exercise and session factors in the R-FPA ($F(1,15) = 11.9$, $p < 0.05$, Holm-corrected) (Fig. 5A and B). Meanwhile, there were no significant interactions or main effects for deoxy-Hb. Oxy-Hb signal change for Stroop interference in all 6 ROIs for EX and CTL conditions are shown in Supplementary Fig. 2.

To clarify the exercise-session interaction in the R-FPA ROI, we calculated the difference of the hemodynamic response due to Stroop interference between post- and pre-sessions. The ([incongruent – neutral] of pre-session – [incongruent – neutral] of post-session) contrast of oxy-Hb signal was calculated for both the EX and CTL groups, separately, and the difference between them was compared. Oxy-Hb signal difference was significantly greater in the EX condition than in the CTL condition ($t(15) = 3.45$, $p < 0.01$, paired *t* test) (Fig. 5C). This result demonstrates that an acute bout of moderate exercise leads to an increased Stroop-interference-elicited cortical activation in the R-FPA.

3.4. Association between behavioral and fNIRS results

We examined the association between the Stroop-interference-related reaction time shortening and R-FPA activation induced by exercise. Conventional correlation analyses were not suitable for the current data: both reaction time and oxy-Hb signals entail substantial individual differences, and a subtraction procedure to contrast out Stroop interference further jeopardizes the quantification of each parameter and narrows the range of parameters leading to a floor effect (Nunnally and Bernstein, 1994). Therefore, we performed a McNemar test: a robust nonparametric procedure, applicable for assessing correspondences between 2 incidences (Siegel and Castekkan, 1988). We examined whether the exercise-induced enhancement of Stroop interference reflected in reaction time coincided with the exercise-induced Stroop interference-related increase of oxy-Hb in a binomial manner. Specifically, the following contrast, ([incongruent – neutral] of pre-session – [incongruent – neutral] of

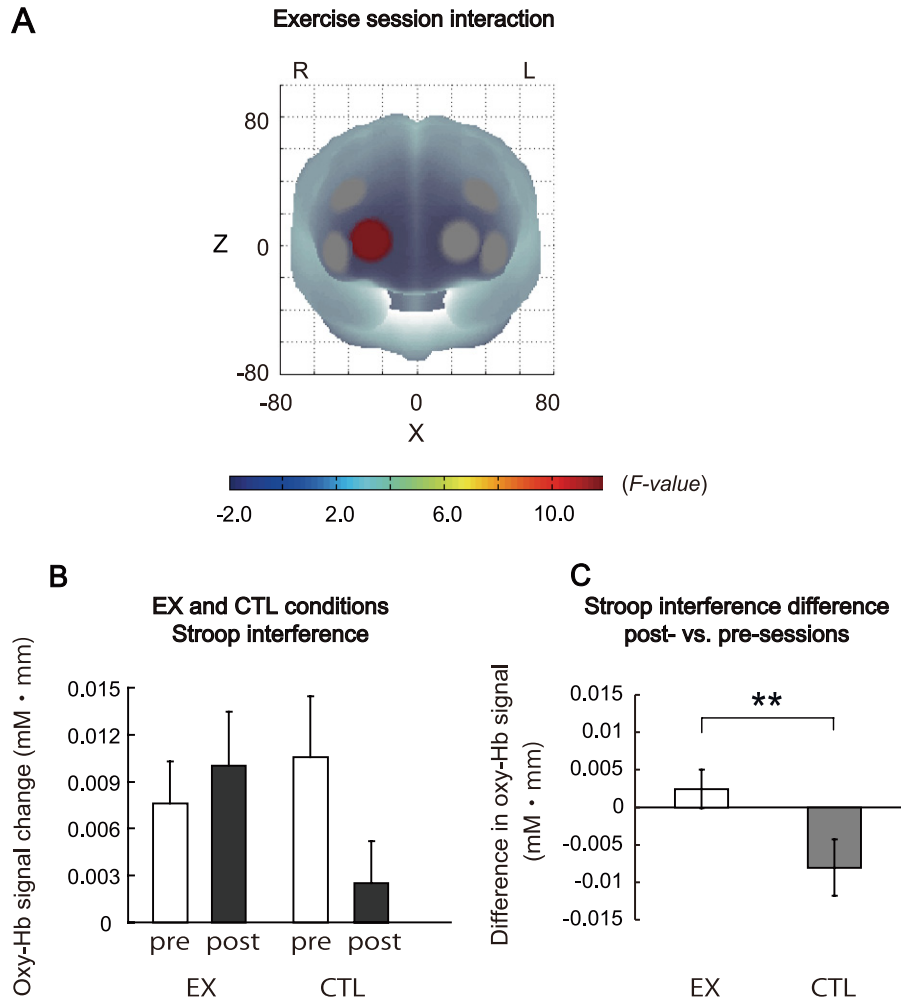


Fig. 5. (A) *F*-map of oxygenated hemoglobin (oxy-Hb) signal change reflecting Stroop interference effect (incongruent – neutral). The interactions between exercise (EX/CTL) and session (pre and post) conditions are shown. *F*-values are shown according to the color bar. Among the 6 regions of interest (ROIs), significant interaction can only be seen in the right frontopolar area (R-FPA) ($p < 0.05$, Holm-corrected). (B) The mean difference of oxy-Hb signals between incongruent and neutral conditions reflecting Stroop interference in the R-FPA for EX and CTL conditions. (C) Stroop interference differences between post- and pre-sessions for oxy-Hb signal contrasts in EX and CTL conditions. Oxy-Hb signal differences in the EX condition are significantly greater than those of the CTL condition ($p < 0.01$). Error bars indicate standard errors.

postsession] in the EX condition – [[incongruent – neutral] of pre-session – [incongruent – neutral] of postsession] in the CTL condition), was calculated for both RT and oxy-Hb signal data, separately, and they were subjected to the McNemar test. This revealed that the frequency of coincidence, as indicated in Table 2, was significant ($\chi^2_{mc}(1,15) = 5.625$, $p < 0.05$). Thus, we concluded that the improved cognitive performance demonstrated in RT reflecting Stroop interference and R-FPA activation elicited by exercise significantly coincided (see Table 2).

4. Discussion

The present study aimed to examine whether an acute bout of moderate exercise induces rapid enhancement of Stroop performance in older adults, and to explore the neural substrate for the plausible cognitive improvement,

focusing on whether it is associated with the task-specific region regardless of age or with the region specific to older adults reflecting compensatory cognitive functions.

Table 2

Contingency table for McNemar test on association between reaction time and oxy-Hb signal

	RT		Total
	–	+	
Oxy-Hb signal			
–	3	1	4
+	9	3	12
Total	12	4	16

Frequency of exercise-induced Stroop interference-related shortening of reaction time and Stroop interference-related oxy-Hb increase in the R-FPA is summarized.

Key: oxy-Hb, oxygenated hemoglobin; R-FPA, right frontopolar area; RT, reaction time.

From the behavioral measurements showing a shorter RT and lower error rate in the neutral compared with that in the incongruent condition, we verified that the Stroop effect could be stably observed for older adults both before and after an acute bout of moderate exercise. Based on this observation, we examined the effect of an acute bout of moderate exercise on Stroop interference, and confirmed significant improvement of performance in RT. Hence, the present study revealed that an acute bout of 10 minutes of moderate exercise enhances cognitive functions to cope with Stroop interference in older adults, presenting experimental evidence for the acute effects of exercise on the executive functions regardless of age. This result is consistent with previous studies that have demonstrated that an acute bout of moderate exercise enhances inhibitory control functions in both younger and older adults (Hillman et al., 2009; Kamijo et al., 2009; Yanagisawa et al., 2010). On the other hand, with regard to error rate, we did not observe a significant exercise effect. Because the change in error rate had a small range of below 8%, it would be an unreliable measure of performance due to the floor effect (Nunnally and Berstein, 1994).

Next we sought the neural substrates for the exercise-induced cognitive improvement in older adults. In presessions, which were compatible with ordinary Stroop task experiments without any exercise effects, we observed significant oxy-Hb signal increases associated with Stroop interference (incongruent – neutral contrast) in the bilateral DLPFC, VLPFC, and FPA in older adults. In contrast, Yanagisawa et al. (2010) reported left-dominant bilateral LPFC activation during corresponding conditions in younger adults. These observations are consistent with a previous fMRI study on the Stroop task with older adults demonstrating that broader prefrontal areas are recruited in older adults than those recruited in younger adults (Langenecker et al., 2004).

With regard to deoxy-Hb, we observed significant deoxy-Hb signal decreases associated with the Stroop interference in only the bilateral DLPFC. The fNIRS apparatus (ETG-7000, Hitachi Medical Corporation) used in the current study utilized 2 wavelengths, 785 and 830 nm. This combination is suitable for detecting oxy-Hb signal, but not optimized for deoxy-Hb signal (Sato et al., 2004; Uludağ et al., 2004). In addition, it is often observed that the oxy-Hb signal is characterized by a higher signal amplitude than the deoxy-Hb signal (Strangman et al., 2002), and this was also the case in the current study (Fig. 4). Therefore, oxy-Hb signal change might have reflected cerebral activity better than deoxy-Hb in the current study.

In the subsequent analysis, we assessed which brain region exhibited changes in activation after exercise, and found that only activation of the R-FPA increased significantly. The increased activation of the R-FPA due to Stroop interference coincided significantly with the improved RT reflecting Stroop interference, providing experimental evi-

dence that the R-FPA is the neural substrate of improved cognitive performance after an acute bout of moderate exercise in older adults.

In the theoretical framework of HAROLD, activation in the contralateral hemisphere is thought to compensate for neural dysfunction specific to task demands (Cabeza et al., 2002; Reuter-Lorenz and Cappell, 2008). For example, while young adults and low-performing older adults recruited similar right PFC regions during a source memory task, high-performing older adults engaged bilateral PFC regions (Cabeza et al., 2002). In a verbal working memory task, younger adults exhibited left prefrontal activation exclusively while older adults recruited bilateral prefrontal areas (Reuter-Lorenz et al., 2000). Moreover, a repetitive transcranial magnetic stimulation (rTMS) study showed that while only right prefrontal stimulation impaired recognition memory function in younger adults, stimulation to either side was sufficient in older adults (Rossi et al., 2004). These studies suggest that additional activity serves a beneficial, compensatory function. The aforementioned fMRI study on the Stroop task with older adults, together with the current study, also demonstrate that contralateral cerebral activation plays an important role in coping with Stroop interference. Most importantly, the current study reveals that an acute bout of moderate exercise enhances compensatory function in the contralateral hemisphere rather than task-specific ipsilateral function. Namely, the acute effects of exercise occurred in a HAROLD manner.

The increased exercise-elicited activation reflecting Stroop interference was most marked in the R-FPA. Although our former fNIRS study enrolling young adults failed to detect R-FPA activation reflecting Stroop interference (Yanagisawa et al., 2010), R-FPA recruitment for Stroop interference has been commonly observed in positron emission tomography (PET) (Bench et al., 1993; Carter et al., 1995; Taylor et al., 1997) and fMRI studies (Milham et al., 2001; Zysset et al., 2001). In addition, a functional connectivity analysis of PET scans revealed consistent task-related connectivity between the L-DLPFC and R-FPA during Stroop interference (Harrison et al., 2005). A recent neuroanatomical examination of rhesus monkeys provided further support for FPA involvement: both the DLPFC and FPA are innervated from the ACC, but the former is enriched with inhibitory neurons while the latter is enriched with excitatory neurons, suggesting differential roles of the DLPFC and FPA in cognitive control (Medalla and Barbas, 2010). This would be likely given the observations that the FPA is typically recruited in complex multitask operations (Badre and Wagner, 2004; Koechlin et al., 1999). However, further investigation is necessary, primarily to elucidate the specific role of the FPA in Stroop interference, and ultimately to understand why the R-FPA is preferentially recruited over the L-DLPFC in the aged brain.

The physiological mechanism behind acute-moderate exercise-enhanced cognitive function remains unidentified. A plausible candidate is the upregulation of brain dopamine

and noradrenalin through exercise, which acts to increase arousal level and leads to improved cognitive functions (McMorris et al., 2008). Moreover, Chmura et al. (1994) proposed the inverted U-shaped function that moderate exercise brings the arousal state to the optimal point for cognitive function whereas weak and strong exercises do not. In the present study, although we did not monitor the metabolism of such neurotransmitters, it is possible that exercising at VT led to increased arousal levels, and hence, improved cognitive performance through the upregulation of such neurotransmitters in the brain. Further studies are necessary to investigate the relationship between exercise-induced brain activation and the metabolism of some neurotransmitters.

Additionally, in the current study, cortical activation related to Stroop interference in most brain regions decreased in the CTL condition. This phenomenon is reminiscent of our previous study on younger adults (Yanagisawa et al., 2010), and is probably attributed to the decreased state of arousal caused by resting between pre- and post-Stroop task sessions. This would clearly augment the apparent effect of exercise, and, at the same time, would add support to our hypothesis that an acute bout of moderate exercise enhances cortical function by increasing arousal.

Another direction that needs to be explored is the missing link between acute and chronic effects of exercise on cognition. Intriguingly, fMRI studies with longitudinal and randomized aerobic exercise trials over 6 months revealed that during a focused attention task, trained older adults, but not controls, recruited the frontal and parietal areas, presumably involved in efficient attentional control. Also, a reduced activation was observed in the dorsal part of the ACC, which would be sensitive to behavioral conflict (Colcombe et al., 2004, 2006). That is, these studies support the view that chronic exercise improves original task-specific functions rather than compensatory functions. These results appear to diverge from the current results, which support the theory that acute exercise affects the cognition of older adults and are in line with HAROLD.

However, while both acute and chronic effects of exercise lead to cognitive improvement, the underlying neural mechanisms may not be the same. Cortical activation patterns for Stroop interference in older adults in the current study clearly demonstrate the occurrence of HAROLD, presumably reflecting a compensatory functional network for performing a cognitive task. Acute exercise might have brought about a temporal enhancement. This would probably be the most efficient short-term solution for utilizing the functional network.

Nevertheless, as Park and Reuter-Lorenz (2009) suggested, compensatory functional networks, as found in HAROLD, are less efficient than primarily honed networks. Thus, long-term efficiency would be best achieved by maintaining or reinforcing the primarily honed functional networks. An interesting possibility is that the acute and

chronic effects are not independent of one another, but, that acute exercise-elicited enhanced compensatory cortical activation might provide some cues toward how primarily honed functional networks can be reinforced. To elucidate how pro-HAROLD acute exercise effects turn into anti-HAROLD effects requires further longitudinal neuroimaging studies focusing on the chronic effects of exercise on cognitive functions of older adults.

In conclusion, the current study reveals that older adults use broad regions of the bilateral PFC to cope with Stroop interference, and suggests that an acute bout of moderate exercise might enhance this ability to cope through increased activation of the R-FPA. The exercise-elicited improvement of executive functions formerly observed in younger adults was reproduced in older adults, but the brain loci responsive to cognitive improvement were different. The current study suggests that, with aging, some contralateral brain loci, such as the R-FPA, begin to compensate for deterioration of the L-DLPFC, which is in line with the HAROLD model, and that acute exercise enhances cortical functions of the compensating region in a pro-HAROLD manner.

Disclosure statement

The authors disclose no conflicts of interest.

All authors hereby declare that they do not have any current or potential conflicts of interest including any financial, personal, or other relationships with other people or organizations that could inappropriately bias this work.

Acknowledgements

This work was supported in part by the Special Funds for Education and Research of the MEXT to H.S., Comprehensive Research on Disability, Health and Welfare from Health and Labour Sciences Research Grants to I.D., and the Grant-in-Aid for Scientific Research from the Japan Society for Promotion of Science (23390354) to I.D.

Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.neurobiolaging.2011.12.022](https://doi.org/10.1016/j.neurobiolaging.2011.12.022).

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