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The association between aerobic fitness and cognitive function in older men mediated by frontal lateralization

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ABSTRACT

Previous studies have shown that higher aerobic fitness is related to higher cognitive function and higher task-related prefrontal activation in older adults. However, a holistic picture of these factors has yet to be presented. As a typical age-related change of brain activation, less lateralized activity in the prefrontal cortex during cognitive tasks has been observed in various neuroimaging studies. Thus, this study aimed to reveal the relationship between aerobic fitness, cognitive function, and frontal lateralization. Sixty male older adults each performed a submaximal incremental exercise test to determine their oxygen intake ($\dot{V}O_2$) at ventilatory threshold (VT) in order to index their aerobic fitness. They performed a color–word Stroop task while prefrontal activation was monitored using functional near infrared spectroscopy. As an index of cognitive function, Stroop interference time was analyzed. Partial correlation analyses revealed significant correlations among higher VT, shorter Stroop interference time and greater left-lateralized dorsolateral prefrontal cortex (DLPFC) activation when adjusting for education. Moreover, mediation analyses showed that left-lateralized DLPFC activation significantly mediated the association between VT and Stroop interference time. These results suggest that higher aerobic fitness is associated with cognitive function via lateralized frontal activation in older adults.

Introduction

A growing number of studies have reported that high aerobic fitness is beneficial for maintaining cognitive functions in older adults (Hillman et al., 2008; Shay and Roth, 1992; van Boxtel et al., 1997). Albeit not many, a few neuroimaging studies have examined the possible neural mechanism underlying the association between fitness and cognition and reported that higher-fitness older adults could recruit task-related brain regions as efficiently and flexibly as young adults do. For example, Prakash et al. (2011) reported that higher aerobic fitness was related to higher task performance in the most difficult condition (eligible-incongruent) of a Stroop task, and they also reported greater bilateral prefrontal activation for the eligible-minus-ineligible incongruent contrast using functional magnetic resonance imaging (fMRI). Because they previously showed that young adults recruited the bilateral prefrontal cortex (PFC) in this condition whereas older adults did not (Prakash et al., 2009), this finding indicates that higher-fitness older adults could recruit more of a task-related brain region to meet a high cognitive demand, as do young adults. Other studies using fMRI have revealed that, when compared with lower-fitness older adults, higher-fitness older adults performing a flanker task exhibited greater task-related activation in the right PFC, and less activation in the left PFC and anterior cingulate cortex (Colcombe et al., 2004; Voelcker-Rehage et al., 2010). Because the right PFC is commonly activated during the flanker task in young adults, the findings of these two studies suggest that higher-fitness older adults could recruit task-specific regions to perform cognitive tasks without relying on compensatory brain activation. However, because the above-mentioned neuroimaging studies did not show any relationship between brain activation and cognitive performance, the holistic relationship of these factors has yet to be elucidated.

As one possible index of brain activation patterns bridging aerobic fitness and cognitive function, evaluation of frontal lateralization is promising. With aging, brain activation patterns during cognitive tasks tend to be less lateralized in the PFC. This phenomenon has been coined HAROLD (hemispheric asymmetry reduction in older adults) (Cabeza, 2002). HAROLD is commonly considered to reflect brain reorganization, which compensates for reduced unilateral neural capacity and efficiency due to age-related structural and physiological decline, and has been found in various tasks. For example, young adults typically demonstrate

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left-lateralized frontal activation during tasks that involve verbal working memory, semantic processing, and recognition memory. Older adults, however, recruit additional contralateral homologous regions of the right hemisphere, a phenomenon that is not present in young adults (Cabeza et al., 1997; Daselaar et al., 2003; Logan et al., 2002; Reuter-Lorenz et al., 2000). Similarly, while young adults show right lateralized frontal activation with tasks that involve spatial working memory, episodic recall, and inhibitory control, older adults engage both the right and left PFC during these tasks (Cabeza et al., 1997; Colcombe et al., 2005; Nielson et al., 2002; Reuter-Lorenz et al., 2000).

The relationship between the HAROLD phenomenon and task performance is still under dispute. As an example of the positive relationship between HAROLD and task performance, in a positron emission tomography (PET) study, Cabeza et al. (2002) found bilateral prefrontal activation for higher-memory older adults whereas only the left PFC was activated in young adults and lower-memory older adults during a source memory task. Likewise, using fMRI, bilateral PFC activation during a verbal working-memory task was found for higher-performing older adults whereas young adults recruited only the left PFC and lower-performing older adults solely recruited the right PFC (Reuter-Lorenz et al., 2000). On the other hand, several studies found the negative relationship between HAROLD phenomenon and task performance. For example, Colcombe et al. (2005) examined individual differences in brain activity and Flanker task performance in young and older adults using fMRI. In young adults, only the right PFC was activated while the bilateral PFC were activated in older adults. Intriguingly, the better performing older adults exhibited more right lateralized activation than the poorly performing ones. Moreover, in an fMRI study employing a go/no-go task, Nielson et al. (2002) revealed that the right prefrontal and parietal cortices were predominantly recruited in young adults while activation was more bilateral in older adults. The greater activation in the left middle frontal gyrus was associated with slower reaction time in older adults.

In light of the findings of the aforementioned studies examining the relationship between aerobic fitness and brain activation during cognitive tasks, we could generally expect that higher-fitness older adults might recruit the PFC as do young adults. In the case of a cognitive task evoking lateralized PFC activation in young adults, we may further expect the possibility that higher aerobic fitness is associated with more lateralized brain activation in older adults, which is to say, a lower degree of HAROLD occurrence in higher-fitness older adults. If this is the case, aerobic fitness could further predict cognitive function via lateralized frontal activation. Because HAROLD is depicted as an increase in bilateral recruitment rather than as an increase in activation in one hemisphere (Cabeza and Dennis, 2012), examining lateralization (difference in activation between both hemispheres) would be more appropriate for evaluating the degree of HAROLD and explaining the neural mechanism of the relationship between aerobic fitness and cognitive function than evaluating each hemisphere separately in older adults.

These two possibilities led us to explore the mediation effect of frontal laterality during cognitive tasks on the relationship between aerobic fitness and cognitive performance. Specifically, we adopted a Stroop task as a cognitive task and examined Stroop-interference-related left-lateralized activity in the dorsolateral prefrontal cortex (left-lateralized DLPFC activation) as an index of frontal laterality using functional near infrared spectroscopy (fNIRS). The Stroop task is suitable for this purpose for two reasons. First, Stroop interference time (time delay between incongruent trials and neutral trials) is very typically used for measuring executive function, which is mediated by the prefrontal cortex, with crucial involvement of the left DLPFC (MacDonald et al., 2000; MacLeod, 1991; Nee et al., 2007; Perret, 1974). Second, aerobic fitness has been reported to be associated with Stroop interference score measured by reaction time (Weinstein et al., 2012), and with those by reaction time and error rate for incongruent-eligible trials in the Stroop task (Prakash et al., 2011).

As a neuroimaging modality, we utilized fNIRS, 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). fNIRS allows subjects to perform tasks in a natural and comfortable environment without being confined to a small, restricted space. In the fNIRS environment, outside influences on cognitive tasks can be kept to a minimum compared to other neuroimaging methods such as fMRI. This is advantageous, especially for measurements involving older adults because they are vulnerable to stress (Bishop et al., 2010; Pu et al., 2014). Indeed, fNIRS has been used to confirm the HAROLD phenomenon in the prefrontal cortex with several cognitive tasks (Heinzel et al., 2012; Tsujii et al., 2010; Vermeij et al., 2012), and thus is suitable for achieving the purpose of the current study.

Ventilatory threshold (VT) was used as the parameter for aerobic fitness. VT is the point where carbon dioxide consumption ($\dot{V}CO_2$) starts to increase more quickly than oxygen uptake ($\dot{V}O_2$) during a graded exercise test in which workload is progressively increased (Beaver et al., 1986). This value has been widely confirmed to be a useful index of aerobic fitness in both patients and healthy normal subjects, and used as indicator for exercise intensity and endurance training effect (Fabre et al., 1997; Sue et al., 1988; Thomas et al., 1985). Conventionally, the highest oxygen uptake a person can achieve during an exhaustive test ($\dot{V}O_{2peak}$) is used as the typical physiological measure for an individual's aerobic fitness level. However, the assessment of an individual's $\dot{V}O_{2peak}$ requires a maximal effort, which might not be warranted in older adults. By contrast, VT can be measured accurately and easily in the general population because VT can be estimated using a submaximal incremental exercise test without placing an unnecessary burden on older adults, who may have medical considerations to take into account, through an exhaustive test (Wasserman et al., 1973).

By using the three above-mentioned variables, we aimed to examine the mediation effect of left-lateralized DLPFC activation on the relationship between VT and Stroop interference time in healthy older adults. We sequentially assessed the following three hypotheses. First, left-lateralized DLPFC activation and VT is related to Stroop interference time. Second, VT is related to left-lateralized DLPFC activation. Finally, the association between VT and Stroop interference time is attenuated or eliminated when left-lateralized DLPFC activation is statistically controlled. Through these analyses, we intend to clarify whether higher aerobic fitness is associated with more lateralized frontal activity for higher cognitive function in healthy older adults.

Methods

Subjects

Sixty older men participated in the current study. Among them, the data for twenty-seven participants has been used in our previous work investigating the effect of a bout of acute exercise on Stroop task performance (Hyodo et al., 2012) and is reanalyzed here from a different perspective. All participants were cognitively normal (screened using the Mini-Mental State Examination, score greater than 23) and psychiatrically normal (screened using the Geriatric Depression Scale, score less than 10) with no history of neurological disorder, psychiatric disorder, or cardiac disorder. They were right-handed native Japanese speakers and had normal or corrected-to-normal vision and normal color vision. 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. Table 1 depicts demographic data of participants.