Possible neurophysiological mechanisms for mild-exercise-enhanced executive function: An fNIRS neuroimaging study

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Abstract Although physical activity or exercise has a beneficial effect on brain structure and function, physical activity levels are decreasing due to sedentary lifestyles in contemporary society. For this reason, there has been increasing attention paid to the practical application of mild intensity exercise, which might be more attractive to and applicable for both young and older adults with a sedentary lifestyle. Indeed, long-term mild exercise training in older adults has been shown to prevent atrophy of the prefrontal cortex as well as moderate-intensity exercise intervention. However, it is still unknown whether acute mild exercise has beneficial effects on brain function, particularly executive function, mediated by the prefrontal cortex, and underlying neural substrates. To address this question, we combined an executive-function task that has been confirmed in many neuroimaging studies to target specific neural substrates and fNIRS neuroimaging techniques that allow the monitoring of task-related cortical activation shortly after exercising. We recently demonstrated that even acute mild exercise can improve executive task performance, which was positively correlated with increased arousal level and also evoked task-related cortical activation on the left dorsolateral prefrontal cortex and left frontopolar area. Although the exact neuronal substrate is still intriguing, animal microdialysis studies have demonstrated that mild exercise increased several neurotransmitters such as acetylcholine and dopamine, which could play an important role in the mild-exercise-elicited higher cognitive function.

Keywords : mild exercise, executive function, fNIRS, arousal, neurotransmitter, prefrontal cortex

Introduction

Numerous studies have revealed that physical activity or exercise can prevent or delay the onset of age-related cognitive dysfunction or neurodegenerative diseases such as dementia^{1,2}). Although it is well known that regular physical exercise increases specific brain volume and function^{3,4}), physical activity levels as well as adherence to regular exercise have decreased over the last decade in Japan. This is probably because it can be difficult to motivate sedentary individuals to participate in and complete a relatively high-intensity exercise intervention due to their low fitness levels and poor adherence rates to regular exercise training^{5,6}). Therefore, there has been an increasing interest in efficient and safe exercise conditions applicable for sedentary people who are known to have a high risk of neurodegenerative disorders later in life.

Despite both young and old people with sedentary lifestyles being highly receptive to mild exercise, the effect of mild exercise on the brain compared to that of moderate or high intensity exercise has not been fully scrutinized. It is only recently that the positive effects of low intensity exercise on the brain have begun to be reported through animal and human studies⁷⁻¹⁰). For instance, our animal studies have revealed that mild exercise is sufficient for improvement of learning and memory functions localized in the hippocampus because it leads to increased hippocampal neuronal activity¹⁰) and neurogenesis^{8,11}) without stress effects. In addition, an MRI study in humans found that a long-term mild-intensity exercise intervention program brought about improvements in cognitive function by alleviating aging-related brain atrophy⁹). However, it is still unknown whether mild exercise can improve executive function, which is to say higher cognitive function mediated by the prefrontal cortex (PFC); and if so, what neural substrates are responsible for these exercise-

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induced beneficial effects on executive information processing.

To address these questions, we adopted an event-related functional near-infrared spectroscopy (fNIRS) neuroimaging method to assess mild-exercise-induced improvements in executive function¹²⁾, given that our recent studies have suggested that increased prefrontal activation can be responsible for enhanced executive performance^{13,14)}. Moreover, we postulated that exercise-induced changes of mood, such as arousal and pleasure levels that could be measured using psychological mood scales¹⁵⁾, might be associated with exercise-induced change in executive function. Thus, combining the fNIRS neuroimaging method and the psychological measurements might provide insight into the possible physiological mechanisms underlying mild-exercise-enhanced executive function. In this short review, we would like to describe the possible neurophysiological mechanisms responsible for mild-exercise-enhanced executive function by eliciting task-related prefrontal activation with an fNIRS method.

Executive function and the prefrontal cortex

Executive function refers to higher cognitive processes related to adequate planning, cognitive control in a conflict situation, anticipation and decision-making, and play a pivotal role in life¹⁶⁾. Several lesion studies and neuroimaging studies have commonly demonstrated that executive function is localized in the PFC^{17,18)}. The PFC can be divided into three sub-regions: dorsolateral (8, 9 and 46), ventrolateral (44, 45, and lateral 47) and frontopolar (10), based on the Brodmann areas, and each region is interconnected with various brain areas processing external information, including sensory systems, cortical and sub-cortical motor systems, the brain stem, as well as internal information from limbic and midbrain sites involved in affect, memory, and reward^{19,20)}. Specifically, dorsal regions of the PFC are highly interconnected with brain regions such as the anterior cingulate cortex (ACC) involved in top-down cognitive control²¹⁾, while ventral regions of the PFC interconnect with limbic systems involved with emotion^{22,23)}. In addition, the PFC also receives neuronal inputs from the brainstem arousal systems²⁴⁾. Therefore, its function could be particularly dependent on changes of neurochemical environments induced by external stimulations such as exercise. From the theoretical concept for acute-exercise/cognition interaction, there has been an increasing amount of evidence that exercise facilitates executive information processing via exercise-released neurotransmitters in the PFC²⁵⁻²⁹⁾. However, it is still unknown how exercise effects neural substrates involved in cognitive processes and, in turn, leads to improved executive function.

Executive function measured using the fNIRS neuroimaging method

There are several cognitive measures of executive function, including the Wisconsin Card Sorting Test, verbal fluency tests, and the Stroop Test. Among them, the Color-word matching Stroop test (CWST) is one of the most extensively used in clinical and experimental settings to measure executive function^{30,31)}. The CWST often consists of three conditions: (1) the neutral condition (e.g., “XXXX” printed in blue ink), (2) the congruent condition (e.g., the name of a color (green, red, etc.) printed in a congruent color), and (3) the incongruent condition (e.g., the name of a color printed in an incongruent color) (Fig. 1). The CWST requires participants to shift cognitive attention onto the color in which the word appears, suppressing the normal tendency of reading the meaning of the word. In the incongruent condition, the autonomic response to read the word, rather than the color of the ink in which the word is printed, elicits a significant slowing in reaction time (RT) called “Stroop effect.”

Many neuroimaging studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have demonstrated regional neural activation in the lateral prefrontal cortex (LPFC) and the ACC in response to the Stroop effect^{21,32-34)}. Unfortunately, these neuroimaging methods are not considered suitable for evaluating transient exercise-induced neural activation because of the nature of their measurement constraints. However, the new neuroimaging method of fNIRS enables functional imaging of brain activity, is compact and thus easy to install and handle in a gym, and allows participants to undertake tasks in a comfortable environment without considerable delay after exercising³⁵⁾. This neuroimaging method measures changes in concentrations of oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb), and allows indirect measurement of neural activation in a superficial layer of the neo-cortex by rely-

Color-word matching Stroop test

Neutral	Congruent	Incongruent
XXXX あお (BLUE)	あか (RED) あお (BLUE)	みどり (GREEN) あお (BLUE)
XXXX あお (BLUE)	あお (BLUE) あお (BLUE)	あか (RED) あお (BLUE)

Fig. 1 Color-word matching Stroop test.

Examples of single trials for the neutral, congruent, and incongruent conditions of the color-word matching Stroop test are exemplified. The words presented were written in Japanese. Translations into English are denoted in parentheses.

ing on neurovascular coupling, which refers to the relationship between neural activity and subsequent changes in regional cerebral blood flow³⁶). Using fNIRS measurements in an event-related manner, Schroeter and his colleagues^{37,38}) demonstrated that the hemodynamic response in the bilateral LPFC was stronger during the incongruent condition compared to the congruent and the neutral conditions of the CWST. Expanding upon their results, we have revealed the neural substrate for acute-moderate-exercise-induced improvement in executive function: elevated cortical activation in the left dorsolateral PFC in young adults and the right frontopolar area in older adults was related to improved Stroop performance^{13,14}). Based on findings of former studies, we hypothesized that acute mild exercise may improve Stroop performance, evidenced by exercise-induced task-related cortical activation.

Mild-exercise-enhanced executive function

Executive function relies on the PFC, and the volume and function of this brain area declines with normal aging. In contrast, there is increasing evidence that regular exercise can improve brain structure and function. For example, aerobic fitness training for 6 months prevented brain volume loss in aging subjects and further increased brain volume compared to a control group³). In addition, participation in regular aerobic exercise training led to increased bilateral anterior hippocampal volume and its related function⁴). These experiments are commonly based on the assumption that improvements in cardiovascular fitness mediate benefits to cognitive ability^{39,40}). In other words, enhanced fitness resulting from aerobic exercise training could affect people's future cognitive abilities. However, the general recommendation for the promotion of fitness and health released by the American College of Sports Medicine is that light intensity exercise, which is equivalent to 30 to 45% of heart rate reserve (HRR) or maximal oxygen uptake reserve ($\dot{V}O_2R$), is advisable for sedentary healthy adults with a low fitness level. This recommendation may be because sedentary people cannot tolerate a relatively higher intensity of exercise, which can elicit negative mood changes.

In fact, recent studies have reported that mild-intensity exercise training produces beneficial improvements in brain structure and function in older adults similar to moderate intensity exercise. For instance, in one study, two years of mild exercise intervention prevented atrophy in the prefrontal regions accompanied with normal aging and increased cognitive function⁹). Moreover, another study revealed that acute mild-intensity exercise consisting of various physical activities such as stretching, flexibility, general mobility, and low-intensity aerobic activity improved performance on a verbal fluency task, which is localized in the PFC, in much older adults⁴¹). However, it is not well known how an acute bout of mild exercise can improve executive function, and what neural changes are

responsible for that enhancement.

So, we examined this question using an fNIRS neuro-imaging method that allows measurement of mild-exercise-induced neural changes in the task-related prefrontal cortex in young adults¹²). We found that 10 minutes of mild exercise led to improved Stroop performance, which was positively associated with exercise-induced increases in arousal. In regards to the neural substrate of enhanced executive performance, we found that acute mild exercise evoked increased cortical activation in response to Stroop interference on the left dorsolateral PFC and the frontopolar area (Fig. 2), which are responsible for strategic top-down control and evaluation of conflict, respectively. Moreover, this cortical activation in both sub-prefrontal regions significantly corresponded with improved executive performance and increased arousal response. Concurrently, this study provides experimental evidence that an acute bout of mild exercise can facilitate executive information processing by exercise-enhanced arousal-related prefrontal activation.

Possible neurophysiological mechanisms responsible for mild-exercise-enhanced executive function

We found a beneficial effect of acute mild exercise on executive function via increased arousal-related cortical activation in the PFC. However, it is not fully understood what neurophysiological mechanisms are responsible for this exercise-elicited cortical activation.

The effects of chronic exercise on the brain and its function mostly reflect durable anatomical changes in the brain at different levels, such as the neuron, synapse, neural network and brain structure levels, through neurogenesis, synaptogenesis, or angiogenesis. In contrast, transient behavioral changes induced by acute exercise occur as a result of transient modulation of the activity of the specific neural networks involved in a certain cognitive task because behavioral changes induced by a single bout of acute exercise appear after the beginning of exercise and disappear relatively quickly within minutes or hours. Thus, based on the results of our previous studies, it is possible to postulate that acute mild exercise leads to improved Stroop performance due to the neural modulation of cortical activation involved in cognitive information processing. If this is the case, it raises the question of what neurophysiological changes are responsible for exercise-induced cortical activation in the PFC.

Several neuromodulators such as cholinergic and some monoamine neurotransmitters could be nominated as neurophysiological components of exercise-induced neural activation (Fig. 3). As we mentioned, the effect of acute exercise on the cognitive process may be closely related to the neuro-modulation of neural networks involved in information processing. For example, the reticular activating system (RAS), which is composed of several neuronal circuits connecting the brainstem to the cortex and regu-

Fig. 2 Mild-exercise-elicited increases of cortical activation in the left dorsolateral prefrontal cortex and the frontopolar area in response to Stroop interference.

Both t-values and F-values are denoted according to the color bars. Among the six regions of interest (ROIs), significant interaction can be seen in the left dorsolateral prefrontal cortex (l-DLPFC) and the left frontopolar area (l-FPA) ($p < 0.05$, Bonferroni-corrected). The bar graphs indicate Stroop interference differences between post- and pre-sessions for oxy-Hb signal contrast in the Exercise and Control conditions. Oxy-Hb signal differences in the Exercise condition are significantly greater than those of the Control condition in both regions (l-DLPFC, $p < 0.001$; l-FPA, $p < 0.01$). Error bars indicate standard error.

Fig. 3 Possible neurophysiological pathways stimulated by an acute mild exercise.

Two groups of projections exist: the cholinergic system and dopaminergic system. The cholinergic system includes the medial septal nucleus (MS), the diagonal band of Broca (DB), and the nucleus basalis (NB), which project to the hippocampus and prefrontal cortex. Dopaminergic system transmits dopamine from the substantia nigra (SN, A9) and the ventral tegmental area (VTA, A10) to the limbic and prefrontal cortex.

lates wakefulness and alertness, could be responsible for exercise-elicited neural activation in the PFC⁴²). Therefore, most exercise neuropsychologists have focused on the noradrenergic system originating from the locus coeruleus (LC), having ascending projections to a large part of the neocortex and hippocampus, because this system is activated under stressful or arousing circumstances^{43,44}. More specifically, the LC is activated by an exercise-induced arousal response of increased noradrenaline (NA) secretion, which in turn will alter neural activation in the PFC^{27,45,46}. In fact, several animal studies using an *in vivo* microdialysis technique have reported that acute exercise leads to increased release of NA in the LC^{47,48}, and that the exercise-induced NA activates several regions of the brain, including the DLPFC, ACC and hippocampus, which are involved in cognitive processes^{43,45,49}. Indeed, we have already found that an acute bout of moderate intensity exercise, which can activate the noradrenergic system, facilitates executive information processing speed by intensifying task-related prefrontal activation in both young and old adults^{13,14}. Unfortunately, this exercise-activated noradrenergic system may not account for the effect of mild exercise, as some researchers have shown that mild exercise is not sufficient to activate the RAS⁵⁰.

Interestingly, recent studies have provided evidence that mild intensity exercise like walking increases acetylcholine (ACh) in the cerebral cortex released from the cholinergic nerve fibers originating in the nucleus basalis of Meynert (NBM)⁵¹. These exercise-induced increases of cortical ACh may contribute to an increase in cortical activation during cognitive information processing, since cholinergic neurons have projection into the cerebral cortex and promote cortical activation related to wakefulness. This assumption is strongly supported by several lines of evidence indicating a relationship between NB activity, ACh, and arousal. For example, greater NB activity is associated with an activated cortex^{52,53}, and stimulation of the NB results in ACh release and electroencephalography (EEG) activation⁵⁴⁻⁵⁶, which reflects the state of behavioral arousal. Moreover, it has been revealed that NB cholinergic nerve activity is also implicated in higher cognitive functions. In humans, both the degeneration of NB neurons and the corresponding losses of cortical cholinergic markers, such as choline acetyltransferase activity, are associated with neurodegenerative diseases accompanied by severe cognitive dysfunctions⁵⁷⁻⁵⁹. Similar views were presented by an experimental animal study demonstrating that deficits in NB neurons and ACh impair performance of specific behavioral tasks⁶⁰. Based on these previous findings, it could be suggested that mild-exercise-activated cholinergic neurons regulating ascending projection of the neurotransmitter ACh to the cerebral cortex are, possibly, the neurophysiological mechanism responsible for enhanced executive function with increased cortical activation in the PFC after an acute bout of mild intensity exercise.

Moreover, the dopamine (DA) neurotransmitter, which is related to motivated behavior, reinforcement, arousal and cognitive control, could be one of the candidates responsible for acute-mild exercise-induced neural activation in the PFC. Dopaminergic neurons mainly originate in the substantia nigra (SN; A9) and the ventral tegmental area (VTA; A10) of the mid brain and project to several brain regions such as the PFC, amygdala, and hippocampus, which play a significant role in motor control, emotion, and decision-making and learning^{44,61}. Interestingly, several animal studies have demonstrated that intense exercise increased the level of DA and its metabolites in the striatum, prefrontal cortex, and hippocampus⁶²⁻⁶⁴. However, it has only recently been suggested that even mild exercise results in increases of dihydroxyphenylacetic acid (DOPAC), a metabolite of DA, in the hippocampus (unpublished data). Actually, we found that work levels (W per day) correlated with the DA metabolite in the hippocampus in the loaded wheel running study (unpublished data). Therefore, it is possible to postulate that acute exercise might activate dopaminergic neurons in a dose-response manner and, in turn, affect cognitive information processing located in the hippocampus and PFC.

Conclusions

Using an fNIRS neuroimaging method, we found that even acute mild exercise can enhance executive function by increasing arousal-related prefrontal activation¹². Although underlying neurophysiological mechanisms have remained elusive, mild-exercise-elicited neuromodulation through cholinergic and/or dopaminergic neurons are most likely a key component of exercise-elicited increases in cortical activation in the PFC, resulting in a transient improvement of executive function. Cholinergic neurons in the basal forebrain as well as dopaminergic neurons in the mid brain are the primary sources of neurotransmitters such as ACh and DA provided to the PFC, which is where executive function is working; and they promote neural activation in response to increased arousal stimulation. Indeed, mild exercise like walking has been found to activate cholinergic neurons and increase extracellular ACh in the cerebral cortex and increase DA metabolite in the hippocampus in animal studies. Further studies are needed to identify the critical role of mild-exercise-activated cholinergic/dopaminergic neurons in arousal and cognition using an antagonist in both humans and animals.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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