

Effect of Exercise on Brain Health

Subjects: **Health Care Sciences & Services**

Contributor: Takeshi Hashimoto

It has been well established in epidemiological studies and randomized controlled trials that habitual exercise is beneficial for brain health, such as cognition and mental health. Generally, it may be reasonable to say that the physiological benefits of acute exercise can prevent brain disorders in late life if such exercise is habitually/chronically conducted.

Exercise

Brain Health

Lactate

1. Exercise Intensity and Modality for Brain Health Regarding Chronic Exercise Adaptation (Implication of Lactate)

To promote and maintain health, the American College of Sports Medicine (ACSM) and American Heart Association (AHA) recommends that healthy adults aged 18–65 years perform sufficient volumes of exercise, such as moderate-intensity exercise for at least 30 min for 5 days/week or vigorous-intensity exercise for 20 min for 3 days/week ^[1]. Importantly, compared to habitual lower-intensity exercise, higher-intensity exercise can effectively improve cardiovascular and metabolic health ^{[2][3][4]}. In particular, long-term/chronic high-intensity interval exercise (HIIE) training (i.e., HIIT) is more effective than long-term/chronic moderate-intensity continuous exercise (MCE) because it increases exercise capacity in addition to cardiovascular and metabolic health in healthy individuals ^{[5][6][7]}. The effectiveness of HIIT over MCE training is also relevant for brain health. Recently, Mekari et al. demonstrated that HIIT was more effective for the improvement of executive function (EF) than MCE training in young adults ^[8]. A recent meta-analysis indicated that HIIT might be more effective for improving severe mental illness (e.g., cognition, negative and positive symptoms of schizophrenia, and depressive mood) than moderate-intensity exercise ^[9]. Given that HIIE produces more lactate than general exercise modalities, such as MCE, some beneficial effects of lactate on health, including brain health, can be implicated. For instance, based on the notion that acute exercise that is favorable for improving brain function is also beneficial for brain health with continuous repetition via chronic exercise training, previous study demonstrated that HIIE could improve EF rather than MCE and was accompanied by more lactate production ^[10], which may imply a potential benefit of lactate on increased cognitive performance by HIIE and subsequent HIIT.

2. Chronic Cognitive and Mental Alterations with Regular Exercise and Its Potential Link to Chronic Exercise-Induced Anatomical and Cerebral Microvasculature Alterations

The potential mechanisms of habitual exercise/physical activity-induced improvement as well as aging-induced impairments in cognitive performance and mental health remain unclear but are assumed to be associated with several physiological factors. For instance, the deleterious effects of aging on the brain comprise negative physiological and anatomical alterations, e.g., hemodynamic activity, synaptic plasticity, decreased brain volume and neurogenesis, while physical activity prevents the deleterious effects on the brain and, in contrast, induces brain neural alterations, including the formation of new neurons, the proliferation of neural cells, and integrated functional neural networks [11][12]. In particular, structural alterations, such as increased neurogenesis, synaptogenesis, angiogenesis, and brain volume, seem to be characteristics of the beneficial effects of chronic exercise on cognitive performance and mental health [13].

Regular aerobic exercise can increase or preserve the regional brain volume in areas associated with cognitive decline and portions of mental health [14][15][16]. It has been reported that aerobic exercise (i.e., 6 to 12 months of a walking program) increases spatial memory as well as gray and white matter volumes in both temporal (including the hippocampi) and prefrontal regions in healthy older adults (without dementia) [17]. In addition, Jonasson et al. demonstrated that following a 6-month exercise training period, the change in “cognitive score” determined by episodic memory, updating, processing speed, and EF was positively related to the thickness of the dorsolateral prefrontal cortex [18]. Regarding mental health, patients with major depressive disorder or schizophrenia show decreased hippocampal or gray matter volume [19][20], while an exercise-induced increase in hippocampal volume can be related to cognitive performance even in patients with schizophrenia [15]. However, whether brain structure is associated with psychiatric and neurological disorders is controversial [21], and whether the positive effects of aerobic exercise can be extended to psychiatric disorders is still unclear [14]. Further studies are needed to uncover the pathophysiology of mental disorders and improve the effect of exercise or physical activity.

In addition to brain structural/anatomical alterations, changes in cerebral microvasculature function can be a physiological factor that may elicit exercise-enhanced brain function. Since the energy reserve of the brain is relatively small, a continuous supply of glucose and oxygen from the cerebral circulation to the brain is required to maintain its function, e.g., cognitive performance. Thus, especially in the brain, synaptic activity suddenly increases the demand for energy for maintaining brain function and consequently might cause a relative lack of oxygen and glucose. However, in the brain, the neural activity causes neurovascular coupling with accordingly transient and adequate increases in regional cerebral blood flow (CBF) and consequently partially maintains brain function [22]. Indeed, the onset of cognitive impairment often occurs following cerebrovascular dysfunction, suggesting that dysfunction of CBF regulation is one of the mechanisms of the onset of dementia [23]. Furthermore, a decrease in the response of regional CBF to a simple motor task occurs when either intracranial carotid arteries or one vertebral artery is occluded in asymptomatic patients [24]. In addition, neural coupling to several physiological stimuli and resting CBF are reduced in patients with Alzheimer’s disease [25][26][27][28][29]. These findings indicate that brain function via neurovascular coupling is attenuated by inadequate global or focal CBF regulation; thus, the regulation of global CBF is important to maintain adequate neural coupling [22] and thus brain function.

3. Can Acute Alterations in CBF to Exercise Affect Cognitive Performance?

As mentioned above, it is expected that maintaining brain function requires adequate CBF regulation as an important physiological factor. However, no study has examined whether alterations in CBF directly modify cognitive performance because CBF cannot be isolated from the many physiological factors that affect cognitive performance in patients with cerebral disease, vascular disease, or dementia, as well as in healthy older adults.

Basically, augmented cerebral metabolism or cerebral neural activity [30][31][32] are accompanied by transient increases in CBF [33][34][35] as well as cognitive performance [36][37] during and/or following mild- to moderate-intensity aerobic exercise. In contrast, similar to the decrease in CBF associated with hyperventilation during prolonged or heavy aerobic exercise [34], the exercise-induced facilitation of cognitive performance disappears during such prolonged exercise [38]. From this background, researchers previously examined for the first time whether manipulation of CBF alteration affects cognitive performance in young, healthy participants [39]. In contrast to the hypothesis, however, cognitive performance improved in response to the decrease in CBF during prolonged heavy exercise, and unexpectedly, an isolated change (i.e., hypercapnia-induced increase) in CBF did not affect cognitive performance at rest or during exercise [39]. Furthermore, several studies reported that increases in CBF during exercise were not directly related to changes in cognitive performance [40][41]. These findings suggest that acute exercise-induced cognitive improvement may not have the same narrative as that of chronic exercise in terms of the cerebrovascular system; thus, it is not simply due to an increase in global CBF, implying that another factor modified by exercise, rather than a change in CBF, affects cognitive performance.

4. Cerebral Lactate Metabolism and Cognitive Performance

A decrease in cerebral oxygenation is induced by prolonged exercise [39][42] or exercise under mild or severe hypoxia [43][44], while impaired cognitive performance is not evident in healthy young participants, suggesting a dissociation between an alteration in CBF and subsequent change in oxygen delivery to the brain and cerebral metabolism or cognitive performance. Indeed, albeit with a reduction in CBF during heavy exercise, the elevation of brain neural activity and metabolism might be accompanied by compensatory increases in the uptake of lactate, glucose, and oxygen support for the brain (arterial-jugular venous difference) [30]. Given that augmented brain neural activity and metabolism are independent of increases in CBF [45], extensive activation of motor and sensory systems due to the higher-order function of the prefrontal cortex may affect cognitive performance rather than cerebral perfusion in response to exercise.

Regarding metabolism, although the brain relies mainly on glucose at rest, during high-intensity exercise, the brain becomes dependent on lactate delivery [46][47] and repeated HIIE, which attenuates the increase in systemic blood lactate, resulting in impaired maintenance of HIIE-enhanced cognitive performance (i.e., EF) [48]. In particular, HIIE may facilitate neuronal activation and excitation levels to the extent that summation is facilitated to improve cognitive performance [10][49][50]. Neuronal activation is associated with an increase in energy requirements due to the transport of neurotransmitters and ions [51], and neurons preferentially utilize lactate as a fuel in vivo [52].

Sustained elevation of arterial/systemic lactate in response to intense exercise promotes the supply of lactate as an energy substrate to meet acute neuronal energy requirements [53][54][55]. In addition, intravenous infusion of 100 mM L-lactate into rats promoted cognitive recovery by preserving cerebral ATP generation following traumatic brain injury [56]. Furthermore, Skriver et al. found a correlation between systemic lactate concentration and the acquisition and retention of motor skills [57]. In addition, lactate supports synaptic activity [58], long-term potentiation and memory formation [59], and neuronal plasticity [60]. These findings suggest that brain function as expressed by cognitive performance depends on the provision of lactate. Indeed, researchers manipulated blood lactate during exercise at a given intensity by repeated HIIE and evaluated whether such manipulation of peripheral lactate metabolism affects brain lactate uptake (i.e., the arterial–jugular venous difference in lactate ($a-v \text{ diff}_{\text{lactate}}$)) and EF [61]. Researchers found that brain lactate uptake is associated with the arterial lactate concentration, and inadequate lactate provision to the brain might attenuate exercise (i.e., HIIE)-enhanced EF [61], irrespective of increased BDNF and catecholamine, both of which are supposed to relate to cognitive performance [50][62][63]. Given the reliance on lactate as a fuel for the brain, variations in blood lactate could affect cognitive performance during and after exercise and account for the significance of exercise (i.e., muscle contraction) for brain function.

On the other hand, a recent study demonstrated that chronic lactate administration to mice promotes hippocampal neurogenesis but does not affect cognitive performance [64]. In addition, Sudo et al. found that recovery of prefrontal oxygenation affected cognitive performance after exhaustive exercise, irrespective of the blood lactate concentration [65]. Further studies are warranted to understand the role of lactate in brain function in acute and chronic exercise.

5. Can Cerebral Blood Flow Regulation That Determines Brain Function Be Modified by Lactate?

Biochemical regulation of the cerebrovascular system by lactate is also evident in an acute setting. Gordon et al. demonstrated in rat brain slices that low oxygen levels facilitated lactate; hence, prostaglandin E_2 (PGE_2) elicited vasodilation [66]. In humans, the CBF response to physiological activation induced by visual stimulation was increased with lactate injection and plasma lactate/pyruvate ratio and subsequently augmented the NADH/ NAD^+ ratio [67]. This increase in lactate/pyruvate and NADH/ NAD^+ ratios may be related to the increase in CBF, probably through nitric oxide (NO) production [68]. In a clinical setting, hypertonic lactate injection increased cerebral perfusion and brain glucose availability and decreased the pulsatility index after acute brain injury [69]. In addition, the brain-injured person is hypermetabolic, and lactate has a pivotal role in supplying energy to bypass the restriction in glycolytic flux and spare limited glucose reserves for other cerebral metabolisms (e.g., pentose phosphate pathway for neuroprotection) (see [70]). Indeed, acute lactate infusion into mild traumatic brain injury patients improved their cognitive function as evaluated by the Mini Mental State Examination (MMSE), with several possible mechanisms, such as the energy substrate effect, the prevention of hyperchloremia, and the reduction in brain cell edema, by restoring impaired brain homeostasis and synapse function after brain injury [71].

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