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Physical activity for cognitive health promotion: an overview of the underlying neurobiological mechanisms

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Abstract

Physical activity is one of the modifiable factors of cognitive decline and dementia with the strongest evidence. Although many influential reviews have illustrated the neurobiological mechanisms of the cognitive benefits of physical activity, none of them have linked the neurobiological mechanisms to normal exercise physiology to help the readers gain a more advanced, comprehensive understanding of the phenomenon. In this review, we address this issue and provide a synthesis of the literature by focusing on five most studied neurobiological mechanisms. We show that the body's adaptations to enhance exercise performance also benefit the brain and contribute to improved cognition. Specifically, these adaptations include, 1), the release of growth factors that are essential for the development and growth of neurons and for neurogenesis and angiogenesis, 2), the production of lactate that provides energy to the brain and is involved in the synthesis of glutamate and the maintenance of long-term potentiation, 3), the release of anti-inflammatory cytokines that reduce neuroinflammation, 4), the increase in mitochondrial biogenesis and antioxidant enzyme activity that reduce oxidative stress, and 5), the release of neurotransmitters such as dopamine and 5-HT that regulate neurogenesis and modulate cognition. We also discussed several issues relevant for prescribing physical activity, including what intensity and mode of physical activity brings the most cognitive benefits, based on their influence on the above five neurobiological mechanisms. We hope this review helps readers gain a general understanding of the state-of-the-art knowledge on the neurobiological mechanisms of the cognitive benefits of physical activity and guide them in designing new studies to further advance the field.

1. Introduction

As people get older, the brain also ages. It has been reported that the brain's capacity to generate new neurons (Spalding et al., 2013) and the volume of the hippocampus (Walhovd et al. 2005; Raz et al. 2005), a brain area where active neurogenesis occurs in adulthood, decreases as people age (after their thirties). Meanwhile, neuroinflammation and oxidative stress increase (Joseph et al., 2005). Accompanying these changes in the brain, cognitive functions including fluid intelligence and memory decline (Li et al., 2004; de Mooij et al. 2018) while the prevalence of Alzheimer's disease, a neurodegenerative disease which constitutes 60-70% of dementia (Barker et al., 2002), increases. In fact, as the world population ages (United Nations 2019), the prevalence of Alzheimer's disease also increases dramatically on a global scale (Nichols et al., 2022). For instance, in the United States, 1 in 10 people aged 65 and over and 1 in 3 people aged 85 and over has been estimated to suffer from Alzheimer's disease (Alzheimer's Association. 2018). What makes the situation worse is that alterations in brain structures and functions may begin over two decades earlier than the symptoms of Alzheimer's disease occur (Alzheimer's Association. 2018). The situation is further worsened by the COVID-19 pandemic such that the pandemic together with governmental lockdowns caused more cognitive problems in both healthy individuals (Allé & Berntsen 2021) and patients with mild cognitive impairment (an early stage of dementia) and Alzheimer's disease (Chen et al., 2021; Gan et al., 2021). Practicing of strategies to enhance brain health, therefore, is an urgent issue from a public health perspective.

Fortunately, decades of research have identified multiple modifiable risk and protective factors of cognitive decline and dementia. Specifically, regular physical activity, non-smoking, a healthy diet, and management of cardiovascular risk factors including obesity and hypertension, among others, reduce the risk of cognitive decline and dementia (Baumgart et al., 2015; Blazer et al., 2015). In this overview, we focus on physical activity given that it is one of the modifiable factors with the strongest evidence (Baumgart et al., 2015).

2. Physical activity for brain health: epidemiological evidence

There have been over a dozen systematic reviews and meta-analyses that investigated the association between physical activity and cognitive functions. In brief, these systematic reviews and meta-analyses consistently identified a positive association between physical activity and improved cognitive function or reduced cognitive impairment. For instance, five meta-analyses of prospective studies that followed up nondemented adults for as long as over 20 years found that in subjects with a high level of physical activity, the risk of cognitive decline was reduced by 35-38% (12 cohorts in Sofi et al., 2011; 21 cohorts in Blondell et al., 2014) while the risk of Alzheimer's disease was reduced by 13-45% (16 cohorts in Hamer & Chida 2009; 26 cohorts in Blondell et al., 2014; 58 cohorts in Iso-Markku et al., 2022; 14 cohorts in Su et al., 2022) and the risk of all-cause dementia was reduced by 14-17% (58 cohorts in Iso-Markku et al., 2022; 29 cohorts in Su et al., 2022). Three meta-analyses of randomized controlled trials (RCTs) with healthy subjects found that exercise training enhances executive functions, attention and processing speed, and memory (effect size=0.123-0.511, 29 trials in Smith et al., 2010; 80 trials in Ludyga et al., 2020; 25 trials in Xiong et al., 2021). Five meta-analyses of RCTs with healthy older adults (over 50 or 55 years old) found that aerobic exercise enhances executive functions, attention and processing speed, and memory (effect size=0.27-0.80, 18 trials in Colcombe & Kramer 2003; 36 trials in Northey et al., 2018; 23 trials in Sanders et al., 2019; 9 trials in Hoffmann et al., 2021; 36 trials in Aghjayan et al., 2022). Interestingly, combing aerobic exercise and strength training may achieve a greater effect size than aerobic exercise alone (Colcombe & Kramer 2003; Northey et al., 2018). Finally, seven meta-analyses of RCTs with people with mild cognitive impairment, Alzheimer's disease, or dementia found that physical activity interventions including aerobic exercise and strength training consistently improve cognitive functions (effect size=0.30-1.12, 30 trials in Heyn et al., 2004; 18 trials in Groot et al., 2016; 11 trials in Song et al., 2018; 13 trials in Jia et al., 2019; 13 trials in Sanders et al., 2019; 16 trials in de Almeida et al., 2020; 16 trials in Cardona et al., 2021).

A single episode of physical activity has also been shown to improve cognitive functions and enhance memory. A meta-analysis of 105 RCTs found that an acute bout of aerobic exercise enhances cognition, no matter whether cognitive tests are administered during exercise, immediately following exercise, or after a delay following the termination of exercise (effect size=0.101-0.108, for the effect during exercise, however, at least 20 minutes of exercise is necessary, Chang et al., 2012). Two meta-analyses focusing on executive functions (28 trials in Moreau & Chou 2019; 19 trials in Ishihara et al., 2021) and one meta-analysis focusing on memory consolidation (22 trials in Wanner et al., 2020) also identified an enhancing effect of acute aerobic exercise (effect size=0.34-0.62 in Moreau & Chou 2019 and Wanner et al., 2020).

Recently, the benefits of physical activity have been reported in higher executive functions, such as creativity (Aga et al., 2021; Chen et al., 2021). A meta-analysis of 28 interventional studies found that both acute (effect size=0.37) and chronic (effect size=0.89) physical activity enhance creative performance (Rominger et al., 2022).

In light of these findings as well as benefits of exercise for physical health, the U.S. Department of

Health and Human Services in its Physical Activity Guidelines for Americans recommends that adults should do at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic physical activity, or an equivalent combination of both per week (U.S. Department of Health and Human Services 2018). For older adults, it recommends that they should adjust their level of effort for physical activity based on their fitness level and that when older adults cannot do 150 minutes of moderate-intensity aerobic physical activity per week due to chronic conditions, they should try to be as physically active as they can (U.S. Department of Health and Human Services 2018). A meta-analysis of 5 prospective studies with aged adults estimated that adhering to the above recommendation (i.e., do a minimum of 150 minutes of moderate-intensity physical activity) is associated with a 40% reduced risk of developing Alzheimer's disease (Santos-Lozano et al., 2016).

3. The exercise physiology

Over a dozen influential reviews (Cotman et al., 2007; Hillman et al., 2008; Hötting & Röder 2013; Voss et al., 2013; Prakash et al., 2015; Basso & Suzuki 2017; Alkadhi 2018; Stimpson et al., 2018; Vecchio et al., 2018; Voss et al., 2019; Stillman et al., 2020; Valenzuela et al., 2020; Walsh et al., 2020; Bliss et al., 2021; Hashimoto et al., 2021; Townsend et al., 2021; Arida & Teixeira-Machado 2022; Sujkowski et al., 2022) and several popular books (Ratey 2008; Chen 2017a,b) have been published to illustrate the neurobiological mechanisms of the cognitive benefits of physical activity. To our knowledge, however, none of them have linked the neurobiological mechanisms to normal exercise physiology to help the readers gain a more advanced, comprehensive understanding of the phenomenon. Below, we would like to address this issue and provide a synthesis of the literature by focusing on five major, most studied mechanisms that underlie the cognitive benefits of physical activity (**Figure 1**). We also try to identify the key, representative references (preferentially focused reviews if multiple studies exist) for each finding.

During physical activity, the body makes a number of adaptations to support endurance capacity or exercise performance, among which are, 1), the release of growth factors such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and vascular endothelial-derived growth factor (VEGF), 2), the formation of lactate (during moderate and higher intensity exercise which surpasses the anaerobic threshold), 3), the release of cytokine interleukin-6 (IL-6), 4), enhanced mitochondrial biogenesis and antioxidant enzyme activity, and 5), release of neurotransmitters such as dopamine and serotonin (5-HT).

During physical activity, BDNF is released from platelets, vascular endothelial cells, and the brain (Walsh & Tschakovsky 2018). BDNF promotes glucose utilization via regulation of insulin secretion (Podyma et al., 2021), enhances lipid oxidation via activation of AMP-activated protein kinase (Matthews et al., 2009), and facilitates tissue repair and remodeling (Kerschensteiner et al., 1999). IGF-1 is released from the liver and skeletal muscle (Barclay et al., 2019) and stimulates carbohydrate and lipid metabolism through its action on insulin and growth hormone (Clemmons 2013). VEGF is released from skeletal muscle, lungs, and the brain (Tang et al., 2010; Hoier & Hellsten 2014). Both IGF-1 and VEGF stimulate vessel growth and tissue repair, ultimately contributing to the maintenance of oxygen supply to muscle and enhanced endurance performance (Eming & Krieg 2006; Ohno et al., 2012; Song et al., 2013; Hoier & Hellsten 2014).

Lactate is produced in muscle cells during glycolysis when the demand for adenosine triphosphate (ATP) and oxygen exceeds supply, a process known as anaerobic glycolysis. Glycolysis is a major metabolic pathway for all cells to generate energy in the form of ATP. Here, glucose is converted to pyruvate and when oxygen is available, pyruvate is decarboxylated to form Acetyl-CoA and feeds into the tricarboxylic

acid (TCA) cycle, another important metabolic pathway, for ATP production. When oxygen is absent such as during moderate and high intensity physical activity, the rate at which oxygen can be taken up into the muscle is insufficient and pyruvate is converted to lactate for ATP production. Although lactate has long been considered a dead-end waste of anaerobic glycolysis, recent research shows that it is involved in the TCA cycle and helps uncouple the carbohydrate-driven mitochondrial energy generation from glycolysis and increases metabolic flexibility (Hui et al., 2017; Rabinowitz & Enerbäck 2020).

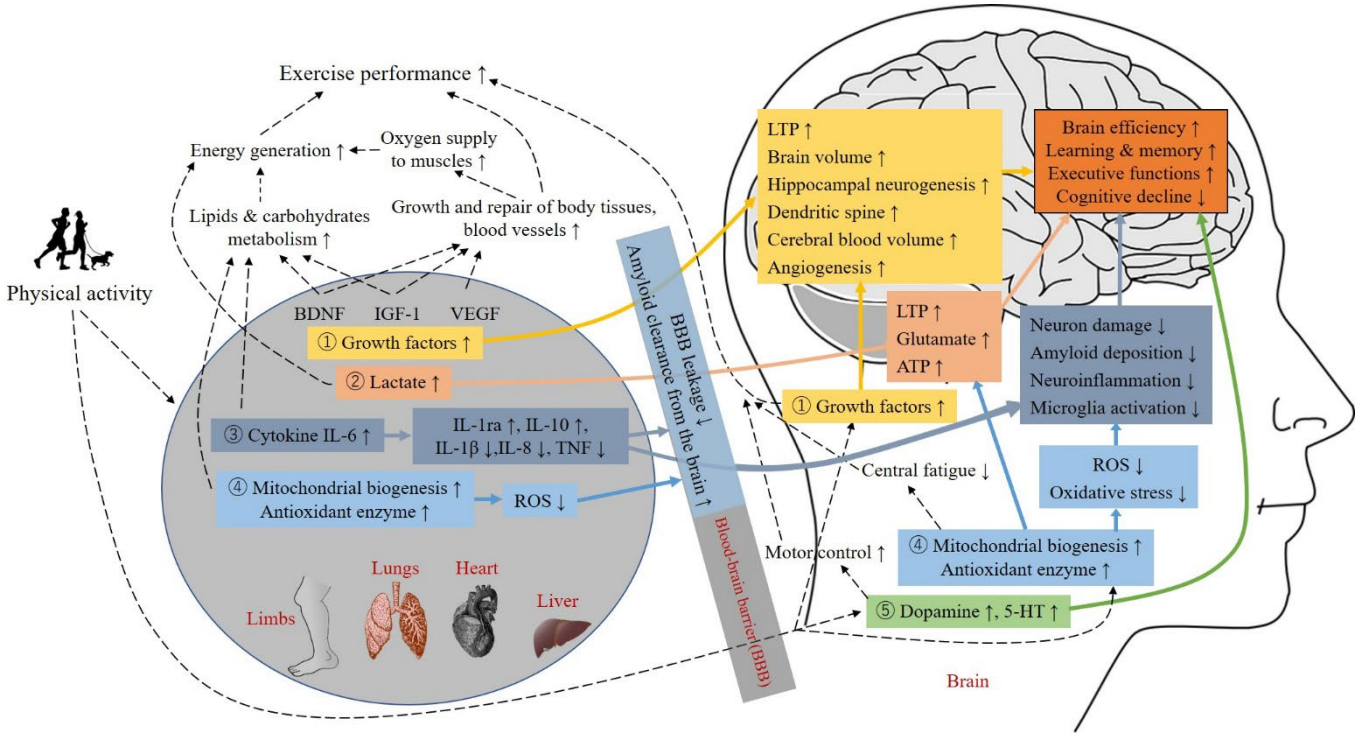

Figure 1. A schematic illustration of the exercise physiology and the neurobiological mechanisms by which physical activity enhances cognition. During physical activity, the body's adaptations to enhance exercise performance (shown by dashed black arrows) also benefit the brain and contribute to improve cognitive performance (shown by solid colored lines, different color is used for each pathway). ATP, adenosine triphosphate; BBB, brain-blood barrier; BDNF, brain-derived neurotrophic factor (BDNF); IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; LTP, long-term potentiation; ROS, reactive oxygen species; 5-HT, serotonin; TNF, tumor necrosis factor-α; VEGF, vascular endothelial-derived growth factor. For details, please see the main text.

During physical activity, IL-6 is also released from skeletal muscle to facilitate lipolysis (breakdown of triglycerides), fat oxidation, and glucose production (Petersen & Pedersen 2005). Furthermore, mitochondrial biogenesis and antioxidant enzyme activity are increased both at peripheral tissues and in the brain (Johnson 2002; Neufer et al., 2015; de Souza et al., 2019). A result of such increase is higher efficiency of energy utilization and enhanced endurance capacity (Neufer et al., 2015). Increased mitochondrial biogenesis in the brain is also believed to delay the development of central fatigue (Steiner et al., 2011), which further enhances exercise performance.

Lastly, the neurotransmitter dopamine (Foley & Fleshner 2008; Wood 2021) and 5-HT (Jacobs & Fornal 1999) are released in the brain for motor control and learning, which also influences exercise capacity.

Research in the past decades suggest that these adaptations to enhance exercise performance also benefit the brain and contribute to improved cognitive performance, as we will discuss in details below.

4. Physical activity for brain health: neurobiological mechanisms

4.1. Growth factors

The growth factor cascade has been the most well-studied mechanism that mediates the physical activity benefits on brain plasticity (Cotman et al., 2007; Hötting & Röder 2013; Voss et al., 2013; Stimpson et al., 2018). Physical activity increases the release of growth factors including BDNF, IGF-1, and VEGF in the peripherals into the blood, which can then pass the brain-blood barrier (BBB) and enter the brain (Poduslo & Curran 1996; Pan et al., 1998). It has to be noted that BDNF is also released by neurons in the brain (Walsh & Tschakovsky 2018) and that during physical activity, muscle contraction secrets two myokines, irisin (Wrann et al., 2013) and cathepsin B (Moon et al., 2016), while liver produces a ketone b-hydroxybutyrate (Sleiman et al., 2016), into the blood which cross the BBB and stimulate the expression of BDNF in the hippocampus. As a result, the brain availability of these growth factors increases.

BDNF is essential for the development, maintenance, and survival of neurons (Chao et al., 2006) and necessary for adult neurogenesis in the dentate gyrus of the hippocampus (Bath et al., 2012). The latter promotes pattern separation (discrimination among similar experiences) and contributes to cognitive flexibility (Deng et al., 2010; Anacker & Hen 2017). BDNF also facilitates long-term potentiation (LTP, Soule et al., 2006), a major cellular mechanism underlying learning and memory (Kandel et al., 2014). IGF-1 (Anderson et al., 2002) and VEGF (Warner-Schmidt & Duman 2008) promote adult neurogenesis in the dentate gyrus of the hippocampus as well, partially via enhancing angiogenesis (i.e., the formation of new blood vessels) given that neurogenesis occurs in an angiogenic niche where sufficient oxygens and nutrients are provided (Palmer et al., 2000). BDNF (von Bohlen und Halbach & von Bohlen und Halbach 2018) and IGF-1 (Dyer et al., 2016) also increase dendritic complexity and promote the growth of dendritic spines, which are the main sites of synaptic input to neurons.

The hypothesis that physical activity-associated improvement in cognitive functions and neural plasticity depends on peripherally released growth factors has been supported by several studies. For instance, treadmill running-induced neurogenesis (Trejo et al. 2001; Glasper et al., 2010) and increase in dendritic spine density (Glasper et al., 2010) in the adult rat hippocampus are inhibited by subcutaneous injection of a serum that blocks IGF-1 from leaving the blood circulation and entering the brain. Similarly, peripheral blocking of VEGF (Fabel et al., 2003) or conditional VEGF gene knockout in skeletal myofiber (Rich et al., 2017) prevents wheel running-induced neurogenesis in the adult mouse hippocampus.

Other studies have demonstrated that physical activity-induced increase in growth factors and neurogenesis in the brain are associated with improved cognitive functions. For instance, infusion of a drug into the hippocampus that blocks BDNF also inhibits wheel running-induced spatial learning benefits in the Morris Water Maze in adult rats (Vaynman et al., 2004). Treadmill running increases both the blood and hippocampal levels of IGF-1 in rats, which are correlated with enhanced spatial learning in the Morris Water Maze (correlation coefficient>0.6, Cetinkaya et al., 2013). Given that wheel running-induced neurogenesis in the dentate gyrus of the adult mouse hippocampus is correlated with the cerebral blood volume (CBV) of the dentate gyrus (correlation coefficient=0.58), the latter has been used as a marker of neurogenesis in humans (Pereira et al., 2007). It was then reported that 12 weeks of aerobic training (ergometer cycling, treadmill running, climbing on a StairMaster, or using an elliptical trainer, 1 hour a time, 4 times a week) increase aerobic fitness (VO_2 max) in human subjects, which is correlated with greater dentate gyrus CBV

(correlation coefficient=0.662), the latter being further correlated with improved performance on a short-term memory test (correlation coefficient=0.62, Pereira et al., 2007). Furthermore, 1 year of aerobic exercise (40 minutes walking at 60-75% maximum heart rate reserve 3 times a week) increases the volume of the hippocampus in older adults by 2%, which is correlated with changes in aerobic fitness (VO_2 max, correlation coefficient=0.37 and 0.40 for the left and right hippocampus, respectively), serum levels of BDNF (correlation coefficient=0.36 and 0.37 for the left and right hippocampus, respectively) and performance on a spatial memory task (correlation coefficient=0.23 and 0.29 for the left and right hippocampus, respectively, Erickson et al., 2011). Since the volume of hippocampus decreases by 1-2% annually in older adults without dementia (Raz et al., 2005), the above result suggests that 1 year of aerobic exercise may be able to reverse aging-related hippocampus shrinkage by 1-2 years (Erickson et al., 2011).

It is worth noting that physical activity increases brain volume and functions not only in the hippocampus, but also in other areas that are responsible for attention and executive functions, such as the prefrontal cortex (PFC). For instance, wheel running increases the number of synapses and dendritic spine density and length in the medial PFC in rats, which is accompanied by enhanced performance on tasks of object discrimination and attentional set-shifting known to depend on the medial PFC (Brockett et al., 2015). In older adult human subjects, compared to a non-aerobic toning and stretching intervention, a 6-month walking intervention (at the intensity of 60-70% heart rate reserve, 40-45 minutes per session, 3 sessions per week) increases the activation of the middle frontal gyrus and superior parietal cortex and decreases the activation of the anterior cingulate cortex, accompanied by improved performance on a selective-attention task (Colcombe et al., 2004). A similar 6-month aerobic training program increases the volume of the PFC and temporal cortex in older adults (Colcombe et al., 2006). In another cohort study, self-reported number of blocks walked over a week is associated with greater volumes of the PFC, occipital cortex, entorhinal cortex, and the hippocampus 9 years later in older adults, which are further associated with reduced risk of cognitive impairment (Erickson et al., 2010). In patients with mild cognitive impairment, a 12-month brisk walking intervention (at the intensity of 75–90% of maximal heart rate or HR_{max}, about 30 minutes per session, 3-4 sessions per week) increases cerebral blood flow in the anterior cingulate cortex, the latter is correlated with improved episodic memory (r^2=0.58, Thomas et al., 2020).

4.2. Lactate

As mentioned above, lactate has long been considered a dead-end waste product of anaerobic glycolysis. However, recent research suggests that lactate is an alternate energy source to glucose for many tissues including muscle, lungs, kidney, as well as the brain (Bergersen 2015; Proia et al., 2016; Magistretti & Allaman 2018; Rabinowitz & Enerbäck 2020). Lactate can cross the BBB via endothelial monocarboxylate transporters and when its level in the blood goes up during physical activity, it is taken up by the brain as an energy source (Van Hall et al., 2009; Bergersen 2015; Proia et al., 2016).

Furthermore, lactate provides precursors for glutamate synthesis, the main excitatory neurotransmitter in the brain (Hertz 2013; Hertz et al., 2014). Glutamine released from astrocytes is considered the predominant source of glutamate in glutamatergic neurons and after being released into the synapse, glutamate is re-uptaken and undergo oxidative degradation in astrocytes. Lactate is converted to pyruvate and used for the synthesis of oxaloacetate and aspartate, two compounds needed for oxidation and synthesis of glutamate, respectively (Hertz 2013). As such, transfer of lactate from astrocytes to neurons is involved in the maintenance of LTP and disruption of endothelial monocarboxylate transporters expression in astrocytes that prevents lactate transport into neurons or inhibition of astrocyte glycogenolysis that prevents lactate production results in impaired long-term memory formation (Suzuki et al. 2011; Newman et al.,

2011; Steinman et al., 2016). The increase of lactate, glutamate, and glutamine following vigorous exercise (≥80% of predicted HR_{max}) in human subjects has been recently confirmed by proton magnetic resonance spectroscopy (Maddock et al., 2011; Maddock et al., 2016). In another study, intense cycling increases the plasma levels of lactate, which is correlated with better acquisition and retention on a visuomotor tracking task (correlation coefficient>0.6, Skriver et al., 2014).

Lactate also increases BDNF and VEGF in the brain. It has been reported that wheel running increases lactate levels in the mouse hippocampus and blocking the transporters of lactate abolishes the wheel running-induced hippocampal BDNF expression as well as enhanced spatial learning in the Morris Water Maze (EI Hayek et al., 2019). In another study, treadmill running-induced increase in VEGF and angiogenesis in the hippocampus and the sensorimotor cortex are absent in lactate receptor HCAR1 gene knockout mice (Morland et al., 2017). Interestingly, subcutaneous injection of L-lactate that mimics the increase of blood lactate levels by treadmill running, increases VEGF and angiogenesis in the brain of wild-type but not lactate receptor HCAR1 gene knockout mice (Morland et al., 2017).

4.3. Inflammation

Although inflammation is essential for proper immunity, excessive and chronic inflammation, which commonly occurs in the aging process, can lead to tissue damage and contribute to the development of neurodegenerative disease such as Alzheimer's disease (Brüünsgaard & Pedersen 2003; Perry 2004; Perry et al., 2010; Heppner et al., 2015). Peripheral pro-inflammatory cytokines (e.g., IL-1, tumor necrosis factor-α or TNF) and macrophages can cross the BBB (Banks et al., 2002) and activate the brain's resident macrophages microglia, which causes neuroinflammation, exacerbates amyloid deposition, and leads to neuron damage (Akiyama et al., 2000; Perry 2004; Perry et al., 2010; Heneka et al., 2015; Heppner et al., 2015; Hansen et al., 2018; Lewcock et al., 2020). Furthermore, systemic inflammation causes damage to the BBB and increases BBB leakage, leading to compromised protection against external toxins, pathogens, and pro-inflammatory cytokines (Varatharaj & Galea 2017; Galea 2021). BBB is also responsible for the clearance of amyloid from the brain into the bloodstream and a dysfunctional BBB contributes amyloid accumulation (Erickson & Banks 2013). Amyloid accumulation in the brain has been considered a key pathology and initiating factor in Alzheimer's disease (Querfurth & LaFerla 2010; Selkoe & Hardy 2016).

Chronic inflammation that causes the above detrimental process is inhibited by physical activity. During physical activity, IL-6 is produced by skeletal muscle to facilitate lipolysis, fat oxidation, and glucose production (Petersen & Pedersen 2005). IL-6 achieves anti-inflammatory effects via stimulating the production of IL-1 receptor antagonist (IL-1ra) and IL-10 (Petersen & Pedersen 2005). IL-1ra blocks IL-1 mediated inflammation (Dinarello 2000) while IL-10 inhibits the production of IL-1α, IL-1β, IL-8, TNF, and macrophage inflammatory protein-α (Moore et al., 1993; Ouyang et al., 2011; Hutchins et al., 2013). IL-10 also controls cellular metabolism in macrophages to limit inflammation by inducing the mTOR inhibitor DDIT4 and preventing glucose uptake, and eliminates dysfunctional mitochondria with low membrane potential and high reactive oxygen species (ROS, Ip et al., 2017).

4.4. Oxidative stress

Oxidative stress occurs when the production of ROS surpasses its clearance and is considered a major contributor to neurodegenerative diseases including Alzheimer's disease (Lin & Beal 2006; Querfurth & LaFerla 2010; Tönnies & Trushina 2017). During the aging process, the mitochondria becomes dysfunctional and the activity of antioxidant enzyme decreases, resulting in increased ROS. ROS causes oxidative damage to lipids, proteins, and nucleic acids including DNA and such damage occurs also in the

major producer of ROS, the mitochondria, which triggers a vicious cycle leading to energy depletion and ultimately cell death (Cui et al., 2012; Tönnies & Trushina 2017). This process occurs both in peripheral tissues and in the brain. Furthermore, increased ROS causes BBB dysfunction and increases BBB leakage, leading to compromised protection against external toxins, pathogens, and pro-inflammatory cytokines and causing further microglia activation, neuroinflammation, amyloid deposition, and neuron damage (Carvalho & Moreira 2018; Song et al., 2020).

To improve endurance performance, physical activity increases mitochondrial biogenesis and antioxidant enzyme activity both at peripheral tissues and in the brain (Johnson 2002; Neufer et al., 2015; de Souza et al., 2019), which help reverse the above vicious cycle. Physical activity also facilitates amyloid clearance via the BBB (Moore et al., 2016; Herring et al., 2016) and the glymphatic system (He et al., 2017). In line with these molecular mechanisms, in animal models of Alzheimer's disease, wheel running inhibits microglia activation and reduces oxidative stress and inflammation in the hippocampus and cortex, which are associated with or accompanied by decreased amyloid deposition and improved spatial learning performance in the Morris Water Maze, Barnes Maze, etc. (García-Mesa et al., 2016; Herring et al., 2016; Lu et al., 2017). Wheel running also reduces the numbers of activated microglia and amyloid deposition and increases the number of dendrites, dendritic spines, and postsynaptic density protein in the cortex and hippocampus in normal aged mice, which is accompanied by enhanced spatial learning in the Morris Water Maze (He et al., 2017). In a longitudinal study of older adults, greater pedometer-measured physical activity is associated with slower amyloid-related cognitive decline and volume loss of gray matter (where neuron cell bodies are located) in the brain (Rabin et al., 2019).

4.5. Neurotransmitters

Two neurotransmitters involved in motor control and learning are released during physical activity, dopamine (Foley & Fleshner 2008; Wood 2021) and 5-HT (Jacobs & Fornal 1999). The increase of these neurotransmitters has been confirmed in many brain regions, including the hippocampus, PFC, stratum, and midbrain (Meeusen & De Meirleir 1995; Chaouloff 1997; Gomez-Merino et al., 2001; Meeusen et al., 2001; Sutoo & Akiyama 2003; Chen et al., 2016).

Dopamine in the PFC plays a critical role in working memory and cognitive flexibility (Cohen et al., 2002; Seamans & Yang 2004; Floresco 2013; Puig et al., 2014; Ott & Nieder 2019) while dopamine in the hippocampus is essential for LTP and the formation of long-term memory (Shohamy & Adcock 2010; Chowdhury et al., 2012; McNamara et al., 2014). Dopamine in the hippocampus also promotes adult neurogenesis in the dentate gyrus of the hippocampus (Takamura et al., 2014; Mishra et al., 2018). Phasic dopamine released from the midbrain dopaminergic neurons is believed to encode reward prediction errors that drive reinforcement learning (Schultz et al., 1997; Schultz 2010; Glimcher 2011; Chen et al., 2015a,b) while tonic dopamine (Collins & Frank 2014; Salamone et al., 2016) and local control of dopamine in the PFC and striatum (Mohebi et al., 2019) invigorate action and support the expression of previously learned behaviors. Furthermore, aging-related loss in dopamine neurotransmission has been associated with aging-related cognitive deficits (Bäckman et al., 2006).

5-HT plays a crucial role in regulating adult neurogenesis in the hippocampus (Alenina & Klempin 2015; Kraus et al., 2017) and one theory argues that the effects of antidepressants especially selective serotonin reuptake inhibitors (SSRIs) are mediated by neurogenesis (Duman et al., 2000; Jacobs et al., 2000; Kempermann & Kronenberg 2003; Sahay & Hen 2007; Eisch AJ, Petrik 2012; Malberg et al., 2021). One mechanism of such influence is likely to be related to BDNF, given there is a reciprocal connection between 5-HT and BDNF such that elevated 5-HT after treatment with SSRIs enhances the expression of BDNF in

the hippocampus and the PFC whereas BDNF promotes the function of serotonergic neurons (Homberg et al., 2014). 5-HT also contributes to associative learning (Dayan & Huys 2009; Seymour et al., 2012; Worbe et al., 2016) and support behavioral control and cognitive flexibility (Crockett et al., 2012; Fonseca et al., 2015; Matias et al., 2017).

The involvement of dopamine and 5-HT in the cognitive benefits of physical activity has been confirmed by several studies. Treadmill running reverses traumatic brain injury-induced decrease in dopamine in the PFC, hippocampus, striatum, and substantia nigra, accompanied by improved short-term memory in a step-down avoidance task as well as spatial memory in the radial-arm maze (Ko et al., 2019). In the same study, treadmill running also increases dopamine in the PFC and improves spatial memory in sham-operation rats (Ko et al., 2019). In a human genetic polymorphisms research, cycling on an ergometer improves cognitive flexibility (shifting between different mental rules) in adolescents, which is associated with a single nucleotide polymorphism (SNP) targeting the dopamine transporter gene DAT1/SLCA6A3 (Berse et al., 2015), supporting the contribution of dopamine to the cognitive benefits of physical activity. Furthermore, in aged adults, 6 months of aerobic training (supervised group exercise including walking, jogging, cycling, cross-training, 45-60 minutes per session, 3 sessions per week)-induced increase in aerobic fitness is correlated with higher levels of dopamine in the stratum ($r=0.34$), as indicated by reduced binding potential shown in positron emission tomography (PET, Jonasson 2017). The latter is further correlated with improved performance on a letter memory task ($r=0.37$, Jonasson 2017). In a cross-sectional study with aged adults, self-reported physical activity intensity is positively associated with dopamine D2/3 receptor availability in the caudate, while the latter is further positively associated with episodic memory (Köhncke et al., 2018).

Regarding 5-HT, it has been reported that treadmill running increases 5-HT and BDNF in the cortex and hippocampus of rats, accompanied by enhanced memory performance in an object recognition test (Pietrelli et al., 2018). Furthermore, wheel running-induced neurogenesis in the dentate gyrus of the adult mouse hippocampus is prevented by tryptophan hydroxylase-2 knockout that causes a lack of brain serotonin (Klempin et al., 2013) or by 5-HT_{3A} receptor knockout (Kondo et al., 2015).

5. Physical activity regimens for brain health

In the light of these neurobiological mechanisms, so what kind of physical activity brings the most benefits? Below we discuss several issues that have been often mentioned in the literature.

5.1. Low, moderate, versus high intensity aerobic exercise

One theory argues that compared to moderate and high intensity, aerobic exercise at low intensity creates a smaller stress response to the body and increases the stress hormone cortisol to a lesser degree, and therefore, may bring more benefits to the brain (Soya et al., 2007). The authors showed that treadmill running at low intensity (15 m/min) elevates blood levels of corticosterone (the primary corticosteroid in rodents) to a lesser degree and increases the expression of BDNF in the hippocampus of rats to a greater degree than that at moderate intensity (25 m/min, Soya et al., 2007). However, against this theory, there is abundant evidence that despite increasing corticosterone, aerobic exercise at moderate to high intensity brings many benefits to the brain (Adlard & Cotman 2004; Schoenfeld & Gould 2012; Chen et al., 2017).

In fact, given that aerobic exercise at higher intensities causes more extensive, emphasized, and long-lasting neurobiological changes (e.g., lactate, serum BDNF, Ferris et al., 2007; Marquez et al., 2015;

Hötting et al., 2016; Boyne et al., 2019; Antunes et al., 2020) and is more effective in improving physical fitness (including high intensity interval training or HIIT, Parikh & Stratton 2011; García-Hermoso et al., 2016), another theory has argued that aerobic exercise at higher intensities may bring more cognitive benefits (Nakagawa et al., 2020). This theory is supported by two meta-analyses of the acute effect of physical activity (Chang et al., 2012; Wanner et al., 2020). Chang et al., 2012 showed that regarding delayed cognitive effects (after more than 1 minute following the termination of exercise, with cognition covering attention, executive function, and memory, etc.), very hard exercise (>93% HR_{max}) has the largest effect size (d=0.465), followed by hard (77-93% HR_{max}, d=0.268), light (50-63% HR_{max}, d=0.245), and moderate (64-76% HR_{max}, d=0.202) exercise. Wanner et al., 2020 found that acute high but not moderate intensity aerobic exercise enhances memory consolidation (effect size=0.40 for non-sleep memory consolidation and 0.44 for sleep-dependent memory consolidation). It is further supported by subsequent studies showing that an acute bout of high intensity cycling (80% HR_{max}) enhances memory performance more than low intensity cycling (<57% HR_{max}) in young adults (Hötting et al., 2016), that self-reported frequency of moderate-to-vigorous intensity physical activity but not walking is associated with better working memory in young adults (Nakagawa et al., 2020), and that engaging in physical activity at higher intensities attenuates the risk of future dementia to a greater degree (Arafa et al., 2021; Feter et al., 2021). However, one meta-analysis found that moderate intensity exercise has a larger effect on the speed of cognition than low and high intensities (McMorris & Hale 2012) while another meta-analysis focusing on executive functions found that the acute effect of high intensity exercise (77-88.5% HR_{max}) is comparable but no superior to moderate intensity exercise (Moreau & Chou 2019). These are perhaps explained by the inverted-U effect of acute exercise on cognitive performance such that an optimal intensity may exist and beyond such intensity, the effect of exercise on cognitive performance may not increase further or even show a decrease (Yerkes & Dodson 1908; McMorris 2016). It has also to be noted that partly due to aging-related decrease in physical fitness, most, if not all, of the RCT studies of chronic aerobic exercise training conducted with older adults used moderate intensity physical activity.

Nevertheless, it is now obvious that even aerobic exercise at low intensities and performed very briefly may provide cognitive and brain benefits, perhaps via different neurobiological mechanisms as compared to moderate and high intensity aerobic exercise. For instance, 10 minutes of very light intensity cycling (30% VO_{2peak}) is able to increase the functional connectivity between the hippocampus and cortical regions, which is correlated with enhance pattern separation (r>0.58, Suwabe et al., 2018). Walking compared to sitting for 4 minutes (effect size=0.70, Oppezzo & Schwartz 2014) or a round-trip stair-climbing for 3 floors compared to using an elevator for the same path (effect size=0.486, Matsumoto et al., 2022) improves creativity in young adults, as measured by a divergent thinking task. In terms of regular aerobic exercise, walking time in a week is associated with higher creativity in young adults (r^2=0.15, Chen et al., 2021) while walking interventions enhance set-shifting and inhibition in sedentary older adults without cognitive impairment (meta-analysis effect size=0.36, Scherder et al., 2014). However, in older adults with cognitive impairment, walking does not improve executive functions (Scherder et al., 2014), suggesting the possibility that to achieve cognitive enhancing effects in clinical populations, aerobic exercise at higher intensities is necessary.

Below, we try to resolve the explanation gap and address the question that aerobic exercise conducted at what intensity brings the most benefits from the perspective of the neurobiological mechanisms. Specifically, we have tried to identify as many as possible relevant human studies that investigated the effects of aerobic exercise on the five neurobiological mechanisms that we discussed above (i.e., growth factors, lactate, inflammation, oxidative stress, and neurotransmitters). The literature search and screening methods as well as all the list of identified studies are available in the Supplementary Material.

The effects of aerobic exercise on the neurobiological mechanisms are shown in **Table 1**. Regarding growth factors, whereas aerobic exercise at high intensity (≥64% VO2max, based on ACSM definition, American College of Sports Medicine 2022) tends to increase blood levels of BDNF, IGF-1 and VEGF, the effect of aerobic exercise at low (~45% VO_2max) and moderate intensity (46-63% VO_2max) is absent, less consistent, or understudied. For lactate, all three intensities increase blood levels of lactate, although a dose-dependent effect exists such that higher intensity increases lactate to a greater degree. Regarding inflammation markers, the effect is most consistent for high intensity on TNF, while the effect of other intensities and on other markers is absent, less consistent, or understudied. For oxidative stress markers, aerobic exercise at all intensities may reduce pro-oxidant markers and increase antioxidant makers, although most studies have focused on high intensity. No study has investigated the influence of aerobic exercise on dopamine or serotonin using positron emission tomography in human subjects.

Therefore, from the perspective of the neurobiological mechanisms, compared to aerobic exercise conducted at low and moderate intensities, aerobic exercise conducted at high intensity is better able to increase growth factors and lactate and reduce TNF and oxidative stress. As such, one may expect that to prevent or reverse aging-associated cognitive decline, aerobic exercise at high intensity is most recommended. On the other hand, aerobic exercise at low and moderate intensities may also increase VEGF and lactate and reduce TNF and oxidative stress, which may explain the findings mentioned above that aerobic exercise at even low intensities may provide cognitive and brain benefits.

Table 1. The effects of aerobic exercise on the neurobiological mechanisms

		Aerobic exercise		
		Low	Moderate	High
Growth factors	BDNF	*ns*[1]	*ns*[1], ↑[2,3]	↑[1,4,5,6,7,8,9]
	IGF-1	*ns*[10,11,12]	*ns*[11,13,14,15], ↑[2,3]	↓[14], *ns*[6,9,14,15,16], ↑[5,7,11,17,18,19]
	VEGF	↑[20]	*ns*[14,21]	*ns*[14], ↑[7,13,14,20,22]
Lactate (dose-dependent[23,25,26])		↑[12]	↑[14,23]	↑[7,14,23,24]
Inflammation	IL-6	↓[27], *ns*[28]	*ns*[29,30,31]	*ns*[29,31,32,33,34], ↑[28]
	IL-10	-	*ns*[31], ↑[35]	*ns*[31,34], ↑[36]
	IL-1β	*ns*[28]	-	↓[37], *ns*[28]
	TNF	↓[28,38], *ns*[27]	*ns*[29,30,31]	↓[9,28,32,33,34,36,37], *ns*[29,31]
Oxidative stress	Pro-oxidant	↓[39]	↓[40,41], *ns*[42,43], ↑[44]	↓[42,45,46,47,48,49,50], *ns*[43,51,52]
	Antioxidant	↑[39]	*ns*[42,43], ↑[41,44,53]	*ns*[43,48,52,54], ↑[42,45,47,49,50]

Exercise intensity is defined based on the ACSM definition, low (~45% VO_2max), moderate (46-63% VO_2max), and high (≥64% VO_2max) (American College of Sports Medicine 2022). Meta-analyses are underlined. ↓, decrease, *ns*, nonsignificant difference, ↑, increase, compared to pre-exercise or control intervention. -, no studies available. Following de Sousa et al., 2017, pro-oxidant markers include thiobarbituric acid-reactive substances, malondialdehyde, F2-isoprostanes, lipid peroxidation, protein carbonyls, 3-nitrotyrosine, hydrogen peroxide, sulfhydryloxidized or thiol group, myeloperoxidase, and POVPC/PGPC; antioxidant markers include superoxide dismutase, total antioxidant status, trolox equivalent antioxidant capacity, glutathione peroxidase, catalase, and glutathione. All markers are measured in serum or plasma. The literature search and screening methods as well as all the list of identified studies are available in the Supplementary Material.

5.2. Aerobic exercise versus strength training

Most of the studies conducted so far have generally focused on aerobic exercise and it is only recently that researchers started to pay attention to strength training, which is also called muscle-strengthening activity or resistance exercise. Available evidence suggests that strength training may bring similar but not superior cognitive benefits to aerobic exercise (Wilke et al., 2019; Broadhouse et al., 2020; Landrigan et al., 2020; Coelho-Junior et al., 2022) and when combined with aerobic exercise, they may lead to greater cognitive benefits (Colcombe & Kramer 2003; Northey et al., 2018).

It has been suggested that strength training may achieve cognitive benefits via distinct neurobiological mechanisms as compared to aerobic exercise. In one study conducted in rats, whereas both treadmill running (aerobic exercise) and ladder-climbing (resistance training) improve spatial learning in the Morris Water Maze, treadmill running primarily upregulates BDNF signaling and ladder-climbing primarily upregulates IGF-1 signaling in the hippocampus (Cassilhas et al., 2012). This finding is consistent with reports in humans that aerobic exercise increases peripheral BDNF to a greater degree and more consistently than strength training (Huang et al., 2014; Szuhany et al., 2015).

We have tried to clarify the effects of strength training on the neurobiological mechanisms by differentiating different intensities. Specifically, by referring to popular guidelines (American College of Sports Medicine 2022; Plowman & Smith 2017), we categorized strength training into three intensities, low (~59% 1 RM), moderate (60-69% 1RM), and high (70~% 1RM). Based on our literature search, the effects of different intensities of strength training on the neurobiological mechanisms are shown in **Table 2**.

In line with the common view (Huang et al., 2014; Szuhany et al., 2015), compared to aerobic exercise (in particular high intensity), strength training does not consistently or reliably increase blood levels of BDNF, even at high intensity (2 out of 6 studies reported a positive effect). In contrast, strength training may increase IGF-1 even at low to moderate intensity (3 out of 5 studies reported a positive effect), the effect of which is absent in aerobic exercise. Strength training may also increase VEGF (2 out of 3 studies reported a positive effect), although the number of studies is still small. Regarding lactate, similar to aerobic exercise, there is a dose-dependent effect and strength training at higher intensities tend to increase lactate to a greater degree. For inflammation markers, strength training may not affect IL-6, IL-10, IL-1 β, and its beneficial effect on TNF is also less consistent compared to aerobic exercise. At high intensity, strength training seems to reduce pro-oxidant markers and increase antioxidant makers.

As such, whereas the ability to increase IGF-1 even at low to moderate intensity is a characteristic effect specific to strength training, the above evidence generally supports the common view that strength training cannot replace aerobic exercise in terms of cognitive and brain benefits (Voss et al., 2019).

Table 2. The effects of strength training on the neurobiological mechanisms

		Strength training		
		Low	Moderate	High
Growth factors	BDNF	*ns*[1,2], ↑[1]	↑[3]	*ns*[1,4,5,6], ↑[7,8]
	IGF-1	*ns*[9], ↑[10,11]	*ns*[12], ↑[3]	*ns*[4,9,12,13,14], ↑[6,10,11,15,16]
	VEGF	-	↑[17]	*ns*[15], ↑[17]
Lactate (dose-dependent[18,23])		↑[18,19,20]	↑[18,21]	↑[18,21,22]
Inflammation	IL-6	*ns*[9]	*ns*[24]	↓[25], *ns*[5,9,14,24,25,26,27,28,29,30], ↑[31]
	IL-10	-	-	*ns*[26,30,32]
	IL-1 β	-	-	*ns*[29,30,32]
	TNF	↓[9]	*ns*[24]	↓[28,29,31], *ns*[6,9,24,26,30,32]
Oxidative stress	Pro-oxidant	↓[33]	*ns*[34]	↓[33,35,36,37,38], *ns*[39,40]
	Antioxidant	↑[33]	*ns*[34]	*ns*[39,40], ↑[33,35,36,37,38]

Referring to ACSM guidelines (American College of Sports Medicine 2022) and Plowman & Smith (2017), resistance exercise intensity is defined as low (~59% 1 RM), moderate (60-69% 1RM), high (70~% 1RM). ↓, decrease, *ns*, nonsignificant difference, ↑, increase, compared to pre-exercise or control intervention.

5.3. Cognitively engaging exercise

Recent research shows that compared to physical activities that involve automated movements such as running and walking, activities that involve multi-limb coordination and simultaneously require attention, cognitive effort, and strategic decision-making may bring greater cognitive benefits (Tomporowski et al., 2015). Examples of such activities include single or team sports such as tennis and soccer, as well as exergames and dance.

A meta-analysis of 20 studies conducted with older adults found that compared to physical activity only, physical activity enriched with cognitive challenges has a larger effect on cognitive functions (effect size=0.16, Gheysen et al., 2018). Another meta-analysis of 18 studies of chronic physical activity training conducted with children found that compared to aerobic physical activity, cognitively engaging physical activity has a greater effect on attention, executive function, and academic performance (effect size=0.53 versus 0.29, De Greeff et al., 2018). A third meta-analysis of 80 RCTs with health individuals including children, adolescents, and adults found that long-term coordinative exercise has a greater effect on cognition than pure endurance and resistance exercise (Ludyga et al., 2020).

Recently, physical training combined with cognitive stimulation has been gaining increasing attention. One such training is exergames. Essentially a motor-cognitive dual task, exergames involve the interaction between the gamer and the game (or device) in which the gamer reacts to cues in the virtual environment provided by the game through his or her body movements. The necessity to respond in a timely, goal-directed and coordinated manner requires multiple cognitive abilities including spatiotemporal perception, attention, and working memory (Oh & Yang 2010; Maillot et al., 2012). Exergames are also more enjoying than pure exercise training (Höchsmann 2018; Farrow et al., 2019), making it a promise candidate for leisure and entertainment. A meta-analysis of 17 RCTs concluded that exergames improve global cognition

(g=0.436), the effect of which is still significant when comparing to traditional physical activity interventions (g=0.435, Stanmore et al., 2017). The effect is observed for both healthy elderly and those with cognitive impairments.

Another cognitively engaging exercise, dance, is also attracting increasing attention. Dance is a performing art that convey ideas (Fraleigh 1987) and involves complex, rhythmic movements that recruit multiple brain areas including those of somatosensory, motor, and cognitive (Teixeira-Machado et al., 2019). In terms of social dancing, it also involves the coordination between two partners. Two recent systematic reviews concluded that dance practice improves various cognitive abilities including attention, memory, and executive functions, which is accompanied by various structural changes of the brain, including increased volume of the hippocampus and white matter integrity (Teixeira-Machado et al., 2019; Muinos & Ballesteros 2021).

Whereas exergames and dance are gaining increasing interest, few studies have investigated their influence on the neurobiological mechanisms. We summarized all the available studies in **Table 3**. As can be seen, two studies investigating the influence of exergames and dance on BDNF, respectively, have reported a positive effect. Exergames and dance also increase lactate, which, however, may depend on the intensity of the specific types of exergames or dance performed. In two studies that evaluated the influence of exergames and dance on inflammation markers, only reduced TNF was confirmed. It remains for future studies to investigate the effects of exergames and dance on IGF-1, VEGF, and other inflammation and oxidative stress markers.

Table 3. The effects of cognitive engaging and mind-body exercise on the neurobiological mechanisms

		Exergames	Dance	Tai Chi	Yoga
Growth factors	BDNF	↑[1,2]	↑[4,5]	↑[9,10]	*ns*[25,26], ↑[27,28,29,30]
	IGF-1	-	-	*ns*[11,12]	-
	VEGF	-	-	-	*ns*[31]
Lactate		↑[3]	↑[6,7]	↑[13]	↑[32]
Inflammation	IL-6	*ns*[2]	-	↓[14], *ns*[11,12,18,16,17,18,19,20]	↓[29,30,33,34,35,36], *ns*[37,38,39], ↑[40]
	IL-10	*ns*[2]	*ns*[8]	*ns*[8,16,17,18,19], ↑[14]	↓[37]
	IL-1ra	-	-	*ns*[16]	*ns*[38]
	IL-1 β	-	-	↓[14,18]	↓[33]
	IL-8	-	*ns*[8]	↓[19,22], *ns*[12,18]	-
	TNF	↓[2]	↓[8]	↓[14,21], *ns*[9,15,16,18,19,20]	↓[30,33,34,36], *ns*[35,40]
Oxidative stress	Pro-oxidant	-	-	↓[14,19,22,23,24], *ns*[18]	↓[29,30,36,41,42,43,44]
	Antioxidant	-	-	↑[14,18,19,22,24]	↑[30,36,41,42,43,44]

↓, decrease, *ns*, nonsignificant difference, ↑, increase, compared to pre-exercise or control intervention.

5.4. Mind-body exercise

Mind-body exercise combines physical activity with mindfulness, in which specific posture and gentle movement are conducted while self-control of attention, thought, and emotion are practiced in a mindful way (Tang et al., 2017). Two most common examples of mind-body exercise are Tai Chi and yoga. Tai Chi

is a traditional Chinese martial art and exercise that emphasizes mind-body connection via appropriate, sequential movements and meditation. Yoga was originated in ancient India and emphasizes body postures and breathing. The mindful meditation component of mind-body exercise has been shown to improve body awareness, enhance attention and emotion regulation, and relieve psychological stress (Hölzel et al., 2011). The benefits of Tai Chi and yoga on cognition have also been confirmed by multiple meta-analyses of RCTs (Lin et al., 2021; Liu et al., 2021; Gothe & McAuley 2015). Consistent with these benefits, a cross-sessional study showed that compared to healthy older women who regularly walk for at least 5 times per week and each time lasting at least 90 minutes, healthy older women doing Tai Chi at a similar frequency have higher gray matter density in the hippocampus, which is correlated with better episodic memory (r=0.547, Yue et al., 2020). In college students, 8 weeks of Tai Chi training increase the gray matter of several brain regions including the superior and middle temporal gyrus to a greater degree than brisk walking (Cui et al., 2019).

We also identified studies that investigated the effects of Tai Chi and yoga on the neurobiological mechanisms (**Table 3**). Whereas both Tai Chi and yoga increase blood levels of BDNF, their influence on IGF-1 and VEGF is not confirmed or unstudied. Furthermore, both Tai Chi and yoga increase lactate. Regarding inflammation markers, whereas both Tai Chi and yoga may reduce IL-1β, yoga is more consistently associated with decreased TNF. Finally, both Tai Chi and yoga reduce pro-oxidant markers and increase antioxidant markers. Importantly, the effects of Tai Chi and yoga on oxidative stress are more consistent than those by both aerobic exercise and strength training. Yoga also decreases TNF more consistently than high intensity strength training (4 out 6 versus 3 out of 9 studies reported a significant effect).

5.5. Green exercise

Another topic gaining increasing interest is the place of doing physical activity, given the abundant evidence on the affective and cognitive benefits of contact with the natural environment (Selhub & Logan 2012; Chen 2018; Chen & Nakagawa 2018a; Miyazaki 2018). Several studies have reported that walking in the natural environment, or so-called green exercise, brings greater cognitive benefits than walking in the urban or indoor environment. For instance, a 50-minute walk along a city street with considerable traffic causes attentional fatigue, as measured by the Necker Cube Pattern Control task; in contrast, a similar walk through fields and woodland in a vegetation and wildlife preserve enhances attention performance on the same task (Hartig et al., 2003). In another study, 1), a 30-minute walk in a quiet residential area without green plants, 2), a similar walk in a park with green plants, and 3), a similar walk besides a canal with green plants all enhance working memory performance on a backward digit span task (Gidlow et al., 2016). However, whereas the effect of walking in a residential area without green plants is limited to immediately after the walk, the effect of walking in a park or along a canal with green plants persists for another 30 minutes after the walk (Gidlow et al., 2016). In a third study, researchers first induced mental fatigue in subjects by asking them to conduct an exhaustive memory task, after which researchers asked the subjects to walk in an urban setting or in an arboretum for 2.8 miles that took about 50 minutes (Berman et al., 2008). It was found that subjects walked in the arboretum performed better on a backward digit span task, indicting better working memory.

Whereas no research has been done to investigate the neurobiological influences of green exercise, studies conducted in the field of nature contact and nature therapy have suggested several potential mechanisms. Green plants produce phytoncides and health-promoting chemicals such as negative air ions and nature contact relaxes the PFC (Ikei et al., 2017; Chen & Nakagawa 2018a). Long-term exposure to green space has been associated with increased neural network efficiency (Lederbogen et al., 2011) and

greater gray matter volume in the dorsolateral PFC and perigenual anterior cingulate cortex (Haddad et al., 2014). In contrast, physical activity in environments with air pollutions such as walking or running along highly traffic-polluted streets may bring negative influences to the body and brain, since pollutants cause neuroinflammation and cerebrovascular and brain damage (Chen & Nakagawa 2018b).

5.6. When physical activity hurts

It has also become clear that excessive physical activity training may cause detrimental effects to the body and brain. Acute exhaustive physical activity and chronic overtraining are two examples. Continuous elevation of blood levels of pro-inflammatory cytokines such as TNF and markers of inflammatory responses such as soluble form of intercellular adhesion molecule-1 (sICAM-1) has been reported 8 hours after a long-distance rowing (160 km, nonstop, Frias et al., 2018), 28 hours after participating in a full or half marathon (Reihmane et al., 2013), and 14 days after a transoceanic rowing race (Keohane et al., 2019). Elevated pro-oxidant markers have also been reported 24 hours after a marathon (Iglesias-Gutiérrez et al., 2021). Similarly, overtraining or excessive exercise training without adequate recovery periods, which often occurs in athletes, can cause skeletal muscle injuries and lead to local and systemic inflammatory responses, including elevated blood levels of pro-inflammatory cytokines (da Rocha et al., 2019). Appropriate strategies to avoid overtraining and promote recovery, therefore, is necessary.

5.7. So what kind of physical activity brings the most benefits? A proposal of targeted physical activity to modulate specific neurobiological mechanisms

Due to a lack of studies on many kinds of physical activities especially low and moderate intensity strength training, exergames, and dance, it is still immature to conclude that we have reached a point where physical activity regimens targeting a specific neurobiological mechanism can be proposed. However, based on the above reviewed evidence, some preliminary inferences may be drawn. In this review, we have presented evidence on 10 types of physical activity, namely, low, moderate, and high intensity aerobic exercise, low, moderate, and high intensity strength training, exergames, dance, Tai Chi, and yoga. To compare the evidence supporting the benefits of each type of physical activity, we calculated an Evidence Consistency Index (ECI), which is the proportion of studies reporting a significant beneficial effect among all the studies available for a specific biomarker. We then used this ECI to rank all the 10 physical activities and picked up the top 3 physical activities for each biomarker (**Table 4**). During this process, we prioritized physical activities with supporting evidence from at least 2 studies. That is, physical activities with only one study available are devalued and considered only when there is a lack of physical activities with at least 2 studies. We admit that setting the prioritizing criterion to “at least 2 studies” is somewhat arbitrary, however, changing it to “at least 3 studies” or “at least 4 studies” affects only part of the ranking.

As can be seen from **Table 4**, high intensity aerobic exercise is the top 1 physical activity that increases BDNF and VEGF and reduces pro-inflammatory marker TNF, while low intensity strength training is the top 1 physical activity that increases IGF-1. Moderate intensity aerobic exercise is the top 1 physical activity that increases anti-inflammatory marker IL-10, while Tai Chi is the top 1 physical activity that decreases pro-inflammatory markers IL-1β and IL-8. Yoga is the top 1 physical activity that reduces pro-oxidant markers and increases antioxidant markers. Summarizing the top three physical activities, whereas aerobic exercise and strength training are the primary activities that promote the release of growth factors, high and moderate intensity aerobic exercise, Tai Chi, and yoga are the primary activities that reduce inflammation. Tai Chi and yoga are also the primary activities that decrease oxidative stress.

Table 4. Top three physical activities with the most consistent evidence for each biomarker based on the Evidence Consistency Index (ECI)

		Top 1	Top 2	Top 3
Grow factors	BDNF ↑	Aerobic High 7/7[a]	Exergames 2/2; Dance 2/2; Tai Chi 2/2	Yoga 4/6
	IGF-1 ↑	Strength Low 2/3	Strength High 5/10; Aerobic High 6/12; Strength Moderate 1/2	Aerobic Moderate 2/6
	VEGF ↑	Aerobic High 5/6	Strength High 1/2	Aerobic Low 1/1; Strength Moderate 1/1
Anti-inflammatory markers	IL-10 ↑	Aerobic Moderate 1/2	Aerobic High 1/3	Tai Chi 1/6
Pro-inflammatory markers	IL-1β ↓	Tai Chi 2/2	Aerobic High 1/2	Yoga 1/1
	IL-8 ↓	Tai Chi 2/4	-	-
	TNF ↓	Aerobic High 7/9	Yoga 4/6; Aerobic Low 2/3	Strength High 3/9
Oxidative stress	Pro-oxidant ↓	Yoga 7/7	Tai Chi 5/6	Strength High 5/7
	Antioxidant ↑	Yoga 6/6	Tai Chi 5/5	Strength High 5/7

ECI is calculated as the proportion of studies reporting a significant beneficial effect among all the studies available for a specific biomarker. a, 7/7: 7 out of 7 studies reported a significant beneficial effect. For simplicity, meta-analytic studies are counted as one single study. Physical activities with supporting evidence from at least 2 studies are prioritized for ranking; physical activities with only one study available are devalued and considered only when there is a lack of physical activities with at least 2 studies. We did not create the ranking for IL-6 and IL-1ra because the evidence for them is generally inconsistent or insufficient.

6. Limitations

There are several limitations of this review. Firstly, we focused five most studied neurobiological mechanisms of the cognitive benefits of physical activity, there are, however, other mechanisms that we do not cover, notably, insulin resistance (Biessels & Reagan 2015; Kennedy et al., 2017), stress hormone regulation (Chen et al., 2016; Chen et al., 2017), epigenetic modifications (Voss et al., 2013; Fernandes et al., 2017), and gut microbiome (Koblinsky et al., 2022). Secondly, in addition to dopamine and serotonin, physical activity also increases the level of other neurotransmitters including norepinephrine and acetylcholine (Basso & Suzuki 2017; Vecchio et al., 2018). In fact, norepinephrine is a central player in the Catecholamines Hypothesis of the acute exercise-cognition interaction which argues that exercise increases circulating plasma catecholamines, which increases the brain availability of noradrenaline and dopamine and contributes to heightened arousal and better cognitive performance (Cooper 1973; McMorris et al., 2016; McMorris 2016; McMorris 2021). Unfortunately, however, little research has been done to directly investigate the involvement of noradrenaline and acetylcholine in the cognitive enhancing effects of physical activity. Thirdly, for simplicity and comprehensibility, we described the involvement of each mechanism primarily in an independent way without making connections among them. Future, more

extensive reviews are needed to cover all these additional mechanisms and their interplay to advance our understanding of the cognitive benefits of physical activity. Lastly, physical activity also promotes mental health and may have therapeutic effects for clinical depression and anxiety disorders (Taquet et al., 2016; Chekroud et al., 2018; Sakai et al., 2021), which is another aspect of brain health. Interested readers may refer to other extensive reviews (Chen et al., 2017; 2018 Physical Activity Guidelines Advisory Committee 2018; Hu et al., 2020) or meta-analyses (Cooney et al., 2013; Rebar et al., 2015; Schuch et al., 2016; White et al., 2017; Klil-Drori et al., 2020) for further information.

7. Conclusions

In this overview, we first summarized meta-analytic reports of prospective and RCT studies on the cognitive enhancing effects of physical activity. We then provided an overview of the exercise physiology and further showed that the body's adaptations to enhance exercise performance also benefit the brain and contribute to improve cognitive performance. Specifically, these adaptations include, 1), the release of growth factors that are essential for the development and growth of neurons and for neurogenesis and angiogenesis, 2), the production of lactate that provides energy to the brain and is involved in the synthesis of glutamate and the maintenance of LTP, 3), the release of anti-inflammatory cytokines that reduce neuroinflammation, 4), the increase in mitochondrial biogenesis and antioxidant enzyme activity that reduce oxidative stress in the brain, and 5), the release of neurotransmitters such as dopamine and 5-HT in the brain that regulate neurogenesis and modulate cognitive functions. We also tried to identify and chart all the available studies of the effects of various types of physical activities on the above five neurobiological mechanisms. By comparing the consistency of supporting evidence for each physical activity, we tried to answer the question that what kind of physical activity brings the most benefits to a specific neurobiological mechanism or biomarker of brain health. In brief, we found that whereas aerobic exercise and strength training are the primary activities that promote the release of growth factors, high and moderate intensity aerobic exercise, Tai Chi, and yoga are the primary activities that reduce inflammation. Tai Chi and yoga are also the primary activities that decrease oxidative stress. We hope this overview may help readers gain a general understanding of the state-of-the-art knowledge on the neurobiological mechanisms of how physical activity benefits cognition and guide them in planning and designing new studies to advance our understanding of such benefits.

8. References

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Supplementary Material

A. Literature search and screening methods

We searched PubMed and Google Scholar using relevant keywords (see below) and also screened available systematic reviews and meta-analyses. Only randomized controlled trials are included and studies that do now allow clear specification of the intensity of aerobic exercise and strength training are excluded. When appropriate meta-analysis exists, we give high priority to meta-analysis and only original studies published later than the meta-analysis are included. For inflammation and oxidative stress, we focused on studies of chronic exercise because the acute and chronic effect of exercise on inflammation and oxidative stress are different and only the chronic effect is believed to play a role in the cognitive and brain enhancing benefits of exercise. Readers interested in the effects of acute exercise may refer to the following reviews for more detailed discussions: Brown et al 2015 Sports Medicine-Open (doi: 10.1186/s40798-015-0032-x); Fisher-Wellman & Bloomer 2009 Dynamic Medicine (doi: 10.1186/1476-5918-8-1); Radak et al 2016 Free Radical Biology and Medicine (doi: 10.1016/j.freeradbiomed.2016.01.024); Tryfidou et al 2020 Sports Medicine (doi: 10.1007/s40279-019-01181-y).

Search keywords for Pubmed:

1, Search field: title/abstract

2, Species: human

3, Language: English

4, Keywords for Table 1: ((exercise OR physical activity OR walking OR running OR cycling OR treadmill OR bicycle) AND (intensity OR vo2 max OR maximal oxygen consumption OR vo2 peak OR peak oxygen consumption OR heart rate)) AND (bdnf OR brain derived neurotrophic factor OR igf-1 OR insulin-like growth factor OR lactate OR inflammation OR il-6 OR il-10 OR il-1 OR il-8 OR tnf OR tumor necrosis factor OR oxidative stress OR oxidant OR antioxidant OR positron emission tomography)

Keywords for Table 2: (strength training OR resistance training OR resistance exercise OR muscle training OR muscle strengthening) AND (bdnf OR brain derived neurotrophic factor OR igf-1 OR insulin-like growth factor OR lactate OR inflammation OR il-6 OR il-10 OR il-1 OR il-8 OR tnf OR tumor necrosis factor OR oxidative stress OR oxidant OR antioxidant OR positron emission tomography)

Keywords for Table 3: (exergame* OR active video gam* OR Dance Dance Revolution OR Nintendo Wii OR Xbox Kinect OR tai chi OR taichi OR tai ji OR taijiquan OR yoga) AND (bdnf OR brain derived neurotrophic factor OR igf-1 OR insulin-like growth factor OR lactate OR inflammation OR il-6 OR il-10 OR il-1 OR il-8 OR tnf OR tumor necrosis factor OR oxidative stress OR oxidant OR antioxidant OR positron emission tomography)

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