The Effect of Exercise on Neurogenesis in the Brain

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ABSTRACT The connection between physical exercise and the brain has long been studied. The evidence showing that physical exercise plays a significant role on neurogenesis and cognitive function has primarily been based on research examining aerobic exercise. In this review, we described three exercise modalities: aerobic, anaerobic, and resistance exercise and their impact on brain plasticity and cognitive function. While each of these exercise modalities have been demonstrated to positively influence brain plasticity and cognitive function, the specific mechanism that stimulates these changes appear to differ to some degree between these training modalities. The effect of aerobic and anaerobic exercise appears to be primarily mediated by changes in expression of brain-derived neurotrophic factor (BDNF), lactate, vascular endothelial growth factor (VEGF), and several additional proteins within the brain. However, resistance exercise appears to influence brain plasticity by myokines such as irisin, insulin-growth factor-1 (IGF1), and BDNF that are secreted from skeletal tissue and stimulate neurogenesis within the brain. In addition to the various training modes, manipulation of various acute program variables such as intensity, volume, and rest intervals leads to numerous possible training paradigms that can provide a different stimulus for neurogenesis. This review focuses on the three primary training modes and their connection to neurogenesis and cognitive function.

IMAJ 2022; 24: 533–538

KEY WORDS: adaptation, anaerobic training, brain plasticity, resistance training

The connection between physical exercise and the brain has been of interest for some time [1]. Most investigations have primarily focused on examining the effects of low to moderate-intensity aerobic exercise and brain function. Exercise is a potent stimulus for brain plasticity, resulting in neurogenesis and psychological health [1]. Participation in an exercise program can reduce symptoms of depression and anxiety while enhancing mood and coping capacity in response to stress [2]. Exercise has also been shown to improve hippocampal memory tasks, such as visuospatial memory [3]. These health benefits are related in part to the role that physical exercise has on stimulating the expression of or increasing the concentration of neurotrophins [4] and its corresponding effect on enhancing neuronal morphology in the brain [5]. Increases in neurotrophin expression, specifically brain-derived neurotrophic factor (BDNF) are associated with improved neuronal morphology [6]. Elevations in BDNF expression following endurance training is reported to stimulate increases in dendritic spine density and dendritic arborization [5,7]. These adaptations have been associated with positive changes in memory and learning [7]. Although exercise appears to have a potent effect on brain neurogenesis, there are numerous training paradigms that can result in varied physiological adaptations, which likely include brain plasticity. Thus, the purpose of this review was to provide some insight into the differences that are known regarding neural plasticity and neurobiology, with specific focus on cognitive function resulting from various training routines.

ENDURANCE EXERCISE AND BRAIN PLASTICITY

Endurance exercise appears to affect brain plasticity by several mechanisms. At the cellular level, exercise enhances hippocampal cell proliferation, stimulates anti-apoptotic pathways, and increases BDNF expression [6]. Morphologically, findings in both human and rodent studies suggest that prolonged physical activity can enhance brain structure and function [8]. It has been well-established that moderate-intensity aerobic exercise increases BDNF levels in rodents, especially in the hippocampus [6,8]. BDNF is part of the neurotrophin family, which has an important role in neuronal remodeling and modulating synaptic plasticity and neurotransmitter release [6]. When elevated, BDNF binds to its receptor tyrosine-related kinase B (TrkB), which activates the cyclic adenosine monophosphate (cAMP)-response element-binding protein (CREB) [9]. CREB activity results in an upregulation of the genes c-fos and JunD that promote neurogenesis and neuronal survival [10]. A study by Park and colleagues [11] reported that mice performing a 12-week (6 sessions per week) endurance exercise protocol experienced a significant increase in neurogenesis and BDNF expression in the hippocampus. This study also noted that aerobic exercise was able to reverse some of the negative effects that obesity had on memory and neurogenesis. Mice fed a high fat diet to cause obesity experienced a reduction in cognitive function and neurogenesis compared to mice that consumed a regular diet. The obese mice that subsequently

performed the aerobic training program were able to reverse the deleterious effects associated with obesity and neurogenesis and cognitive function.

Aerobic exercise is also reported to increase the proliferation of brain endothelial cells and increase angiogenesis [12,13]. Exercise-induced angiogenesis (e.g., the formation of new blood vessels) results in an increase in capillary density within the brain. Angiogenesis induces the sprouting of new capillaries from pre-existing vessels is a mechanism that has been suggested to be specific to the endurance training effects on brain function [12,13]. Previous studies have reported a positive association between angiogenesis, brain function, and neurogenesis [12,13]. This finding was supported in part by a study examining mice that had the protein pentraxin 3 (PTX3), an angiogenesis regulator, removed [13]. The investigators reported significantly greater neuronal loss, significant decreases in vessel proliferation, and impaired restoration of cerebral blood flow after ischemic stroke in PTX3 deficient mice compared to control mice. Other investigators demonstrated that brain PTX3 levels are upregulated after a stroke, promoting recovery by enhancing angiogenesis [12]. Elevated PTX3 expression resulted in an increase in newly formed blood vessels and an increased expression of vascular endothelial growth factor receptor 2 (VEGFR2).

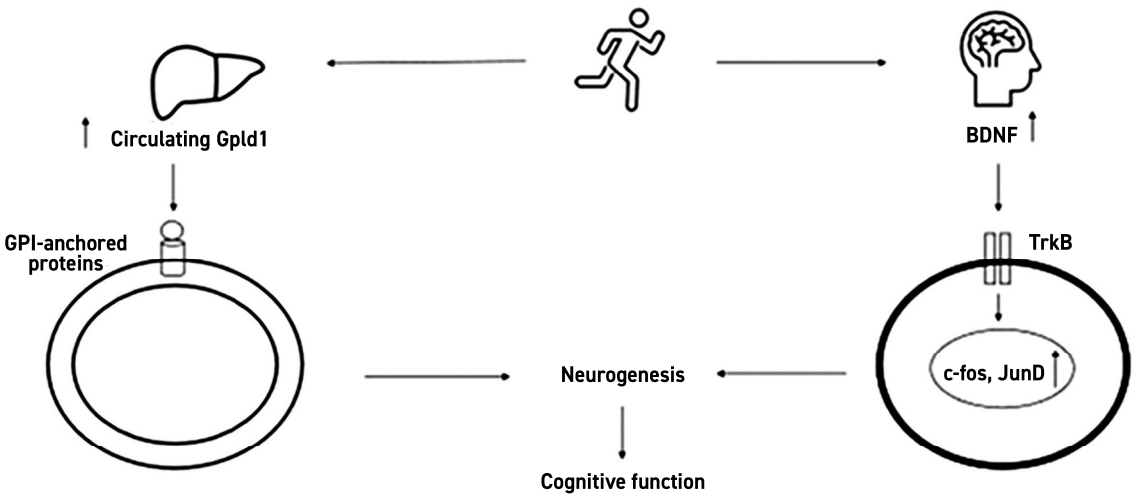
Recent evidence has also suggested that there may be a potential liver-to-brain axis link to exercise-induced cognitive benefits. Horowitz and colleagues [14] indicated that increases in glycosylphosphatidylinositol (GPI) phospholipase D1 (Gpld1), a hepatic enzyme responsible for releasing membrane-bound GPI-anchored proteins from the cell surface, has been shown to improve cognitive function and neurogenesis. It was demonstrated that aged mice that were injected with the plasma of exercising mice exhibited an increase in the number of neurons in the dentate gyrus region of the hippocampus compared to control sedentary aged mice. In addition, the mice that were injected with the plasma of exercising mice experienced significant improvements in learning and memory as measured by the radial-arm water maze. The investigators identified Gpld1 protein as a blood factor that increased after exercise and was likely responsible for the increase in cognition and neurogenesis. Figure 1 provides an overview of the mechanisms that are thought to stimulate neurogenesis as the result of chronic endurance training.

EXERCISE IS A POTENT STIMULUS FOR BRAIN PLASTICITY AND NEUROGENESIS

ENDURANCE EXERCISE AND COGNITIVE FUNCTION IN HUMANS

The positive benefits associated between neurogenesis and cognitive function in animal studies is well-documented. However, technological limitations minimize the ability to examine neurogenesis in humans. Thus, the positive effects associated with aerobic exercise on cognitive function and behavior is a function of enhanced neurogenesis. This finding is supported by numerous investigations. Song and Yu [15] examined 120 subjects that were randomized into either a moderate-intensity aerobic activity group or a health education program control group. The investigators reported that participants who performed the aerobic exercise program had significantly greater improvements in cognitive function and health-related quality-of-life measures than the control group [15]. A recent meta-analysis examining 13 randomized controlled studies with a sample size of 673

Figure 1. Mechanisms associated with neurogenesis resulting from endurance training
Gpld1 = glycosylphosphatidylinositol phospholipase D1, BDNF = brain derived neurotrophic factor, GPI = glycosylphosphatidylinositol, TrkB = tyrosine-related kinase B



subjects diagnosed with Alzheimer's disease (AD) showed that aerobic exercise intervention significantly improved cognitive function compared to control subjects [16]. An additional meta-analysis examining 27 studies with a total of 2077 subjects with mild competitive impairment (MCI) reported that physical exercise significantly improved global cognitive function, executive function, and delayed recall [17]. Interestingly, the investigators of this latter investigation indicated that moderate-intensity aerobic exercise had a greater effect on cognitive function than both low- and high-intensity aerobic exercise for subjects with MCI.

ANAEROBIC TRAINING AND BRAIN PLASTICITY

In contrast to aerobic training, which is performed at a sub-maximal intensity, anaerobic exercise is performed at a high-intensity that is unable to be sustained for more than a couple of minutes. A common method for anaerobic training involves the use of repeated sprints or other high intensity activity that is interspersed with lower intensity activity or rest. This type of workout is called high-intensity interval training (HIIT). HIIT has been shown to induce secretion of the pro-angiogenic vascular endothelial growth factor (VEGF) [18]. Increases in VEGF are thought to be stimulated by elevations in blood lactate from exercising muscle [18]. Increases in lactate concentrations from exercising muscle interacts its receptor, hydroxycarboxylic acid receptor 1 (HCAR1), found on endothelial cells in the brain [19]. Morland and colleagues [18] investigated the effect of HIIT on angiogenesis by having mice perform a HIIT program consisting of five training sessions per week for 7 weeks. Each training session consisted of 10 high-intensity intervals of 4-minutes each separated by a 2-minute active rest. The investigators reported significant increases in VEGF and capillary density in the dentate gyrus of the hippocampus compared to sedentary mice. The investigators also observed that lactate injections, equal in concentration to that experienced by the animals after the HIIT program, resulted in similar improvements in VEGF and capillary density. The authors were also able to identify the receptor mediating this effect by knocking out HCAR1 and observing no increase in angiogenesis by either exercise or lactate injection.

HIGH-INTENSITY INTERVAL TRAINING MAY HAVE A GREATER EFFECT ON NEUROGENESIS AND COGNITIVE FUNCTION THAN LOWER INTENSITY, CONTINUOUS EXERCISE

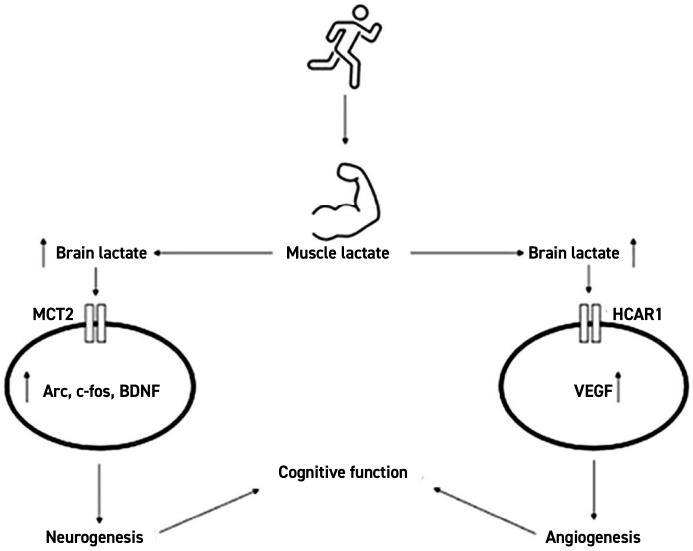
Lactate elevations are increased by a greater magnitude from high-intensity exercise than moderate-intensity exercise. Whether this results in a differing effect for neurogenesis is not well-understood. In neurons, lactate increases the expression of several genes related to synaptic plasticity such as Arc, c-fos, and BDNF [20]. One study showed that injection of lactate at levels similar to that observed following high-intensity exercise enhanced adult hippocampal neurogenesis [21]. However, when mice were treated with an antagonist to the lactate monocarboxylate transporter 2 (MCT2) the effect of lactate on neurogenesis was attenuated. These results indicate that increases in circulating lactate concentrations enhance hippocampal neurogenesis in an MCT2-dependent manner.

VEGF appears to also play a significant role in the neurogenesis pathway. Fabel and co-authors [22] reported that exogenous treatment with VEGF to neural stem/progenitor cells isolated from the adult rat hippocampus elevated neurogenesis. This effect was reversed by blocking the VEGF receptor. This study also demonstrated that exercising mice injected with the VEGF antagonist experienced a significant decrease in neurogenesis. Another investigation using a murine model reported that 8-weeks of HIIT was significantly more effective at increasing brain plasticity markers like VEGF and TrkB compared to moderate-intensity continuous training [23]. A recent investigation demonstrated that a HIIT program consisting of 10 sets of 30-second running separated by a 2.5-minute recovery period enhance neurogenesis to a greater magnitude than moderate intensity continuous training [24]. This study also observed a significantly greater increase in BDNF expression in the hippocampus compared to the sedentary group, which was not observed in the moderate-intensity continuous training group. Although both moderate-intensity aerobic training and HIIT in rodents have been shown to increase neurogenesis [14,22,24], a limited number of studies suggest that high-intensity anaerobic exercise may be superior to lower intensity continuous exercise. Figure 2 depicts the mechanisms that are thought to stimulate neurogenesis as the result of chronic anaerobic training.

ANAEROBIC TRAINING AND BRAIN FUNCTION IN HUMANS

The benefits of aerobic training on cognitive function have been well-documented [15-17]. However, there are several investigations that suggest that HIIT has an even greater impact than lower intensity continuous aerobic training [25,26]. HIIT has been shown to result in greater increases in circulating BDNF concentrations compared to moderate-intensity training [25]. A recent study by Reycraft and co-authors [25] compared sprint interval training, consisting of four 30-second all-out running bouts interspersed with 4-minute rest intervals, to moderate-intensity continuous training (e.g., 30-minute running at 65% VO_2max), and high-intensity continuous running (30-minutes at 85% of VO_2max). The investigators reported significantly greater elevations in BDNF concentrations following the sprint training compared to the two continuous training running protocols. Ben-Zeev and colleagues [26] examined the effects of a combined 3-month anaerobic exercise and resistance training program in adolescents and reported significant greater improvements in spatial learning, pattern separation, and inhibitory control compared to age-matched participants performing a moderate-intensity endurance training program only. Based on the available evidence it appears that anaerobic training may

Figure 2. Mechanisms associated with neurogenesis resulting from anaerobic training
BDNF = brain derived neurotrophic factor, MCT2 = monocarboxylate transporter 2, VEGF = vascular endothelial growth factor



have a greater impact on neurogenesis and cognition compared to lower intensity aerobic training.

RESISTANCE EXERCISE AND BRAIN PLASTICITY

Resistance exercise requires an individual to move a resistance through the complete range of motion of a muscle. Resistance training has been shown to be a potent stimulus for increasing BDNF concentrations [27]. Skeletal muscle, the largest organ in the human body, systemically secretes myokines essential for cognitive function, such as BDNF, irisin, and insulin-growth factor-1 (IGF-1). When released from the muscles, these myokines can cross the blood–brain barrier and influence brain function [28]. As a result, exercise-induced increases in circulating concentrations of these myokines have been shown to upregulate and promote neurogenesis, neuronal survival, and neuroplasticity as well as to enhance cognitive function [29].

THE BENEFICIAL EFFECT OF RESISTANCE EXERCISE ON BRAIN PLASTICITY AND COGNITIVE FUNCTION IS POSITIVE AND, TOGETHER WITH THE IMPROVEMENT TO BONE AND MUSCLE HEALTH, MAY MAKE THIS MODE OF TRAINING IDEAL FOR MOST POPULATION GROUPS

Resistance training is a potent stimulus for increasing circulating BDNF and IGF1 concentrations [27,30-32]. IGF-1 is an important neurotrophic factor that has both neuroprotective and angiogenic properties. IGF-1 elevation in the brain leads to greater neuronal proliferation, survival, and plasticity [31]. Resistance training has been reported to increase circulating IGF-1 concentrations to a greater magnitude than endurance training [30]. Cassilhas and colleagues [32] compared the effect of both resistance exercise and aerobic exercise on changes of IGF-1 in the hippocampus and in the peripheral circulation. While both exercise modalities showed improvement in spatial learning and increase BDNF and IGF-1concentrationsin the hippocampus, significant elevations in circulating IGF-1 concentrations and an up-regulation of IGF-1 receptor expression in the hippocampus was noted in the resistance training group only.

There have been several investigations with rodents that indicated that resistance training may be a potent stimulus for increasing BDNF and irisin expression in the brain. Lee et al. [33] reported significant elevations in BDNF levels in the hippocampus and significant improvements in spatial learning in animals that performed resisted wheel running compared to animals that performed the wheel running unloaded [33]. Kim et al. [34] trained mice on a climbing ladder three times per week for 12 weeks and reported significant elevations in circulating irisin concentrations compared to sedentary mice. Irisin has previously been shown to be an essential factor for neural differentiation in embryonic stem cells [35]. Inhibiting irisin expression in neuronal precursor cells has also been demonstrated to inhibit the differentiation of mice embryonic stem cells into neurons [35]. Irisin's role with regard to brain plasticity is also supported by the observation that overexpression of irisin levels in the brain can enhance synaptic plasticity and memory in AD mice [29]. Resistance training has shown to have significantly greater elevations in circulating irisin concentrations compared to an aerobic training program [34].

The effect of resistance exercise and neuroplasticity has been examined in a limited number of investigations. A recent investigation by Liu et al. [36] incorporated a 4-week resistance training program (four sessions per week of ladder climbing with progressive resistance) in mice with AD and reported significant improvements in cognitive function, decreased neuroinflammatory

markers, and enhanced synaptic plasticity, compared to a sedentary control group. In addition, the study also demonstrated an increase in synaptic markers such as synaptotagmin 1 and synaptobrevin in the hippocampus of the resistance exercised group. These synaptic markers appear to be essential in enhancing neural connections, leading to long-term potentiation (LTP) in synapses [37].

Another study using a similar resistance training design examined the effects of resistance exercise on neuroplasticity and cognitive function [30]. In that study, rodents were injected with intraventricular lipopolysaccharide to induce MCI. The animals were trained three times per week for 6 weeks. Each training session consisted of eight sets with a progressive increase in load. The investigators reported a significant elevation in the synaptic plasticity marker synapsin in the dentate gyrus of the hippocampus and improved spatial learning compared to the sedentary group.

We found only one investigation that has examined the effect of resistance training on neurogenesis. In that study mice were divided into a resistance training (e.g., climbing a ladder), endurance training (e.g., treadmill running) group for 14 weeks (5 training sessions per week) or a control group [38]. Neurogenesis was determined by the number of doublecortin-positive cells count (DCX+) in brain sections. While both the exercise groups experienced greater levels of neurogenesis than the control group, the resistance training group was noted to have significantly higher DCX+ positive cells than the other two groups.

Most research examining the effects of exercise on brain plasticity has primarily focused on cardiovascular exercise. Based on the available evidence, resistance training appears to have a significant effect on brain plasticity, which may differ from lower intensity, continuous cardiovascular exercise. Figure 3 shows the mechanisms that are thought to stimulate neurogenesis as the result of chronic resistance training.

RESISTANCE EXERCISE AND BRAIN FUNCTION IN HUMANS

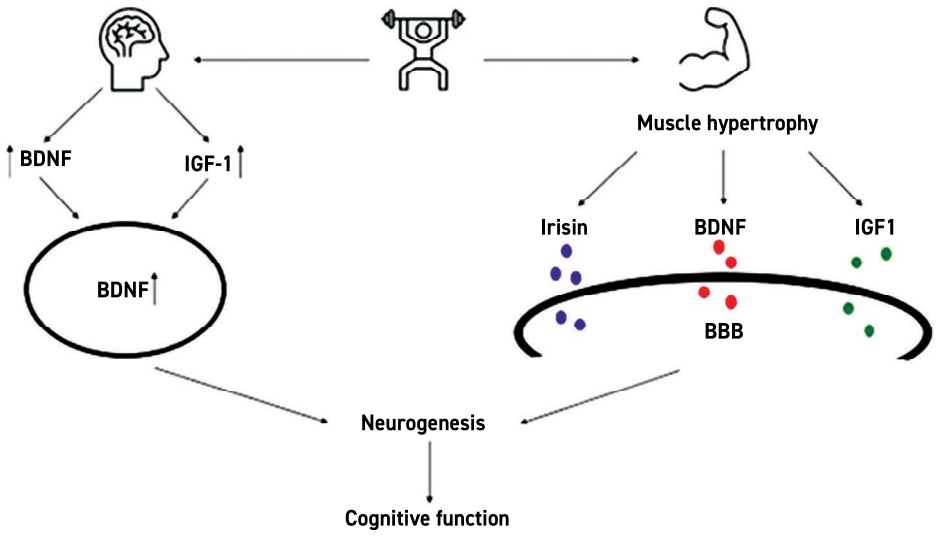
Resistance training has been shown in several investigations to improve working memory and executive function [39,40]. Additional forms of resistance training have also been shown to enhance cognitive function [39,40]. A 12-week elastic band-based high-speed power training in older women with MCI was reported to result in significant improvements in cognitive function and physical performance compared to a low-speed strength training group [39]. A similar study on overweight or obese community-dwelling patients with schizophrenia showed that a high-velocity circuit resistance training performed twice a week for 8-weeks significantly improved cognitive function and reduced psychiatric symptoms [40].

Although the research examining resistance exercise and neurogenesis is limited, the studies that are available have been consistent in demonstrating a positive benefit on improving cognitive function and stimulating increases in several neurotrophic factors associated with brain plasticity.

CONCLUSIONS

The beneficial effects of physical exercise on brain plasticity and neurogenesis are conclusive. Most research examining exercise and brain plasticity has focused on continuous aerobic exercise. However, all modes of training (e.g., aerobic, anaerobic, and resistance exercise) appear to be potent stimulators of brain health. Recent investigations have indicated that high-intensity training may have a greater advantage in affecting neo-

Figure 3. Mechanisms associated with neurogenesis resulting from resistance training
BBB = blood–brain barrier, BDNF = brain derived neurotrophic factor, IGF-1 = insulin-like growth factor 1



genesis and cognitive function than lower intensity, continuous exercise. In addition, initial studies on the effect of resistance exercise on brain plasticity and cognitive function is quite positive and together with the benefits associated with resistance training and bone and muscle health, may make this mode of training ideal for most population groups. Further research on the benefits associated with these training modes is warranted.

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