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Effects of Physical Exercise (Type, Intensity, Duration) on BDNF and Cognitive Functions in the Hippocampus of Adults and Elderly: A Literature Review

Upik Rahmi[1,*], Hanna Goenawan[2], Nova Sylviana[2], Setiawan[2], Septian Andriyani[1], Suci Tuty Putri[1], Lisna Anisa Fitriana[1]

[1]Faculty of Sport and Health Education, Universitas Pendidikan Indonesia, Bandung, 42095, West Java, Indonesia
[2]Faculty of Medicine, Universitas Padjadjaran, Bandung, 40132, West Java, Indonesia

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Abstract The hippocampus has a function in forming memory mediated by the BDNF neurotrophic that has been induced by physical exercise. Several studies have been conducted to determine the effect of exercise on BDNF and cognitive function (learning, memory, and executive function). The effect of exercise is influenced by the type, intensity, and duration. Purpose: To review the effect of physical exercise by type, intensity, and duration on BDNF and cognitive function in adults and the elderly. This study used the literature review method from several databases, including PubMed, Science Direct, and Cinahl, from 2010 to 2021. Certain keywords were used to search articles; PICO was also used in screening articles, extract, and analysis of data. Results: There are eleven articles included in this literature review. Aerobic exercise increases blood circulation to the heart and brain, so VO_2max increases. Training intensity causes hemodynamics, cellular metabolism, and memory formation, while exercise time influences the hypothalamic response. These mechanisms were interrelated in the effect of exercise on the concentration of BDNF as a mediator of synaptic plasticity. Conclusion: BDNF and cognitive function in the hippocampus are affected by physical exercise, especially the type, intensity, and duration of training.

Keywords Exercise, Hippocampus, BDNF, Cognitive Function, Executive Function, Memory, Adult, Elderly

1. Introduction

The hippocampus is essential in learning, memory formation, and consolidation [1]. During the aging process, there is a decline in cognitive functions, where the structure of the brain decreases, especially in the frontal, parietal, and temporal lobes [2], which is characterized by a progressive loss of cognitive function (memory, spatial learning and executive processes [3]. Memory on cognitive function is influenced by neurotrophin Brain Derivative Neutropic Hormone (BDNF), which supports nervous system survival, growth, and synaptic plasticity in the hippocampus [4]. Neurotrophic factor (BDNF) is an adaptive response of brain metabolism as a signaling molecule in the formation and maintenance of synapses to modulate synaptic plasticity related to cognition in the hippocampus because brain plasticity is capable of structural and functional changes in the nervous system in response to experience, and also functions as a mediator of physical activity that causes changes in plasticity brain [5,6]. Physical exercise increases neurogenesis, synaptogenesis, angiogenesis, and release of the neurotrophin BDNF as a neural mechanism mediating cognitive effects [7].

Research evidence that physical exercise can improve cognitive function by increasing hippocampal neurogenesis in adults to prevent neurodegenerative diseases in the elderly, where routine physical exercise affects executive function and speed of information processing in adults as well as at age after 60 years, physical activity can improve executive function, memory, spatial learning at high fitness levels [6,8].

The exercise dose affects cognition, where working memory is improved by dynamic training at moderate intensity and short duration [9]. High intensity increases the speed of processing and activation of the brain during memory retrieval. So many studies have discussed that physical exercise can function as neuroprotective, especially in the elderly [10,11].

2. Method

The author conducted an extensive search using several major electronic databases. These include PubMed, ScienceDirect, and Cinahl. The examination consists of studies published in English. The primary author searched article titles and abstracts by entering the keywords “exercise,” “physical activity,” “hippocampus,” “BDNF,” “Cognitive,” “adult,” and “Elderly or Old.” Review articles were also used as a resource to seek additional studies. A citation was downloaded into an Excel spreadsheet, and full-text articles were obtained for all studies entering the review.

The author processes the data by identifying each study’s research methodology and characteristics, including category, sample, study design, study results (i.e., physical activity, cognitive function, BDNF), research intervention including type, intensity, and duration of intervention, study results, and conclusions. After that, the data is extracted and then synthesized.

3. Result

Table 1 summarizes the effect of exercise on BDNF included in this literature review. The five articles chosen for this research were used to compile a table. While table 2 shows the literature result on exercise's effect on cognitive function.

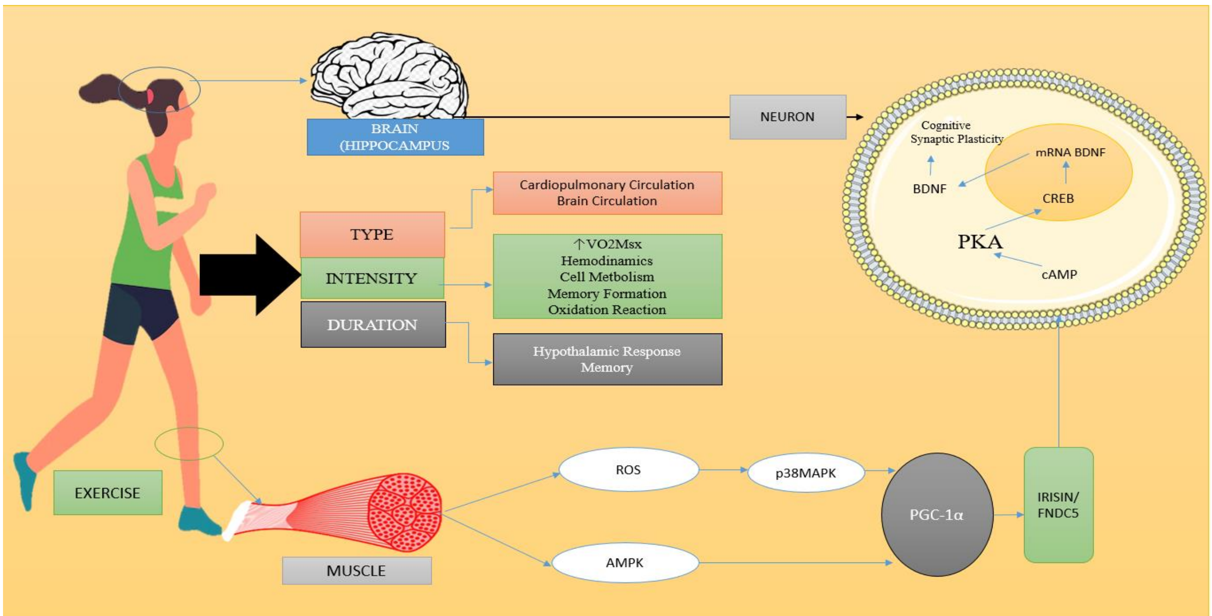

Figure 1. Effect Physical Activity at BDNF and Cognitive Function

Table 1. Effect of Exercise on BDNF

Author	year	Participants (human, rats Aged, n)	Exercise Training (Type)	Exercise Intensity	Duration	Result	Noted
Denisa M áderov á, et al(16)	2019	elderly, 69, n = 22	acute exercise cycling	moderate (65–75% HR max)	60m/minute with a 40-minute session for three months	BDNF	The absence of changes in serum BDNF in the elderly at rest and physical exercise
Louis Nuvagah Forti.,et al(17)	2015	elderly male and female (68-73 years) n=56	Resistance Training	hight (80%1RM) low (20%1RM)	high intensity; 3x a week with each session of 2x10-15 repetition, low-intensity 2xa week with each session of 80-100 repetition. Both were carried out for 12 weeks	BDNF in male	there was no difference in BDNF at high and low intensity in women and men; BDNF increased more in men than in women
Su-Youn Cho.,et al(18)	2019	female, 65 years (n= 37)	taekwondo	moderate (50– 80% HRmax)	Five times per week, each session 60 minutes for 16 weeks	BDNF	exercise increases BDNF to help the growth and survival of nerve cells and neurotrophic factors that regulate synaptic plasticity.
Chloe Rezola-Pardo.,et al(19)	2014	Adult male and female, n=126	walking	Hight moderate low	Three times a week with high intensity 20 minutes, moderate-intensity 15 minutes, low power 5-10 minutes, for three months	BDNF	Changes in BDNF during the intervention were not significantly associated with physical exercise
Anne Maass a,b,.,et al(10)	2016	elderly 60-77 years, n = 21	treadmill	low	3 times a week, with each 30 minute session for 3 months	BDNF	exercise modulates hippocampal plasticity and memory

Table 2. Exercise Effects on Cognitive Function

Author	year	Participants (human, rats Aged, n)	Exercise Training (Type)	Exercise Intensity	Duration	Result	Noted
Xiao-Qin Wang.,et al(20)	2016	female,wistar rats (8 weeks), n = 50	treadmill	high	High intensity with 30m/minute, moderate-intensity 20m/minute, low intensity 15m/minute with each 40 minutes session, 5-7 days/week, for 30 days	working memory, memory spatia	all intensity improved accuracy
				moderate			
				low			
Chien-Heng Chu., et al. (7)	2015	older adults n=46	cycling	Hight (85% HRmax)	2-4 circuits, each session 3 minutes, 150kpm/minute with a 100/200 cycle ergometer for 25 weeks	executive function	a good level of fitness can maximize the good cognitive effect (cognitive performance processing speed) caused by acute exercise
Mauro Giovanni Carta.,et al(22)	2021	elderly aged 65 years, n= 120	aerobic	Moderate 0-59%Hrmax)	Three times a week, with each session of 65 minutes for 12 weeks	memory	cognitive function improves in male
Natalie Frost.,et al (23)		Elderly, female 69 years, n-99	cycling	moderate	Two times a week with every 100-minute session for six months	executive function	there is no difference in executive function in moderate and high exercise
	2020			high			
Louise-Ann Leyland. et al. (24)	2019	older adult female 50-83 years, n=100	cycling	low	90 minutes a week for eight weeks	executive function	physical exercise cycling pedal cycle and e-bike have the effect of increasing physical activity so that it can improve cognitive function
Tadahiko AMEGAYA.,et al(25)	2014	elderly 65 years, n= 58	physical and leisure activities were	moderate	Three times a week with each session of 45 minutes for 12 weeks	executive function	Community-based physical exercise can improve cognitive function in the elderly

4. Discussion

Figure 1 illustrates mechanisms of type, intensity, and duration of exercise to increase BDNF and cognitive function by activating glucose uptake in skeletal muscle cells, increasing phosphorylation of protein kinase (AMPK) by activating AMP, and increasing reactive oxygen species (ROS). Activation of p38 mitogenic-activated protein kinase (MAPK), in response to increased muscle activity, stimulates transcription of the PGC-1α gene as part of the skeletal muscle adaptation mechanism. Then PGC-1α modulates the proteolytic cleavage of the type III fibronectin precursor protein containing the FNDC5/irisin protein. Irisin stimulates the accumulation of cyclic adenosine monophosphate (cAMP), activation of cAMP-dependent protein kinase (PKA), cAMP response element-binding protein (CREB) phosphorylation, and expression of brain-derived neurotrophic factor (BDNF). This mechanism can lead to synaptic plasticity and cognition.

4.1. The Role of Exercise Types on BDNF for Nervous System Homeostasis

Acute and regular exercise improves cognitive function in humans and rodents by increasing BDNF concentrations in the medial temporal lobe [12]. The American College of Sports Medicine(ACSM) defines aerobic exercise as using large, rhythmic, and sustained muscles. Muscles will metabolize aerobically during aerobic exercise. Cycling, dancing, hiking, taekwondo, jogging/distance running, swimming, and walking are some types of sports that are included in aerobic exercise [9]. Including gymnastics developed from brain vitalization exercises known as A-Pik (anti-senile) exercises can improve the cognitive abilities of the elderly [13].

While, anaerobic exercise is defined as a physical activity performed continuously and intensively. In the short term, anaerobic does not use oxygen as the primary energy source [14]. Both types of exercise have positive effects on determining heart and brain health, especially the hippocampus as a cognitive center. Several studies have shown that exercise results on cognitive and BDNF vary depending on the intensity of the exercise [14,15].

Physical exercise on cognitive function in the hippocampus [16] via the effects of muscle exercise is mediated by the transcriptional coactivator PGC-1α [17]. Irisin will induce glucose uptake in skeletal muscle cells, increase protein kinase (AMPK) phosphorylation by activating AMP and inhibit AMPK, which will block glucose absorption. Irisin can also increase reactive oxygen species (ROS). In addition, irisin starts p38MAPK in an AMPK-dependent manner [18]. Akimoto et al.'s study suggested that activation of p38 mitogenic-activated protein kinase (MAPK), in response to increased muscle activity, stimulates transcription of the PGC-1α gene as part of the skeletal muscle adaptation mechanism. Activation of the p38MAPK pathway in C2C12 myocytes stimulates PGC-1α activity. Otherwise, it is blocked by specific p38 inhibitors. Activation of p38 in mice increases PGC-1α protein expression in fast-twitch skeletal muscle [19]. PGC-1α induces FNDC5 expression in primary and hippocampal neurons [20]. Irisin, a glycosylated protein hormone, is also released into the blood circulation [18] [20]. Irisin is produced in skeletal muscle to regulate biological processes in energy metabolism and extracellular division, and then irisin is secreted into the blood [21,22]. Irisin enters the central nervous system through the blood-brain barrier (BBB) and induces the expression of BDNF as an essential neurotrophic mediator triggered by exercise and produced in the brain, where BDNF functions as neuroprotective and neuroplastic [23].

Animal studies have shown that vigorous exercise increases the structural and functional plasticity of the hippocampus by increasing the generation of mature neurons (adult neurogenesis) in the hippocampal dentate gyrus, increasing dendritic complexity and spine density, and increasing synaptic plasticity [24].

4.2. Role of Intensity of Exercise on BDNF and Cognitive

The intensity of exercise is generally divided into low intensity, moderate intensity, and high intensity regarding the proportion of maximum heart or VO_2max [25]. VO_2max is used as an indicator of cardiorespiratory fitness. High-intensity exercise, or High-Intensity Training (HIT), is known as a movement with maximum intensity (above 80%) [14,16]. HIT resulted in a more significant increase in VO_2max than moderate-intensity exercise [26].

One of the training models is Hight Interval Intensity Training (HIIT). HIIT is characterized by several cycles of vigorous activity, usually lasting 30 seconds, followed by periods of rest or low-intensity exercise, generally lasting more than 1 to 5 minutes. Intervals in HIIT purpose to maintain exercise performance [27].

Research on exercise-induced changes in BDNF is dependent on exercise intensity. This supports the findings of Chole Rezola Pardo. et al. 2014 with 5 minutes of low-intensity walking, 15 minutes of moderate, and 20 minutes of high intensity, which did not show a significant increase in BDNF because walking at all three intensities was insufficient to increase BDNF secretion [28]. However, in a 2019 study by Sun Yon Cho et al., it was found that moderate-intensity taekwondo physical exercise 50-80% HRMax significantly increased BDNF neurotrophin and cognitive function [29]. Likewise, Ferris et al. reported that when subjects performed 30 min of cycling below 20% of the ventilation threshold concentration level (55% VO_2max), there was no significant difference in their serum BDNF levels. Still, when they performed 30 minutes of cycling at ventilation rates higher than the 10%

threshold concentration (75% VO_2max), their serum BDNF levels increased significantly [30].

Therefore, high-intensity aerobic exercise is believed to increase the concentration of BDNF at rest. Máderová et al. specifically investigated the effects of acute and long-term cycling exercise in young adults [16]. They found cognitive function and BDNF increased through acute training and a transient increase in BDNF expression levels in motor response to long-term aerobic exercise. So it can be concluded that BDNF and cognitive function increased after aerobic exercise. The intensity of exercise can increase BDNF so that it causes 50% VO_2max [19].

The intensity of exercise is an essential element that influences several physiological functions, for example, hemodynamics, cellular metabolism, and oxidation reactions [20]. Specific studies on exercise intensity and cardiorespiratory fitness suggest in older adults that high-intensity aerobic exercise improves executive function (EF) [21]. Moderate aerobic exercise that was acute for executive function showed more minor differences between congruent and incongruent [18]. These benefits can be attributed to the exercise-induced increase in cerebral blood flow [23,24]. Increased brain neuron activity and metabolism during exercise result in increased cerebral blood flow [30]. Treadmill exercise can improve long-term spatial and working memory; low-intensity benefits short-term working memory, and medium or higher-intensity benefits long-term memory. In research, exercise intensity affects memory performance [12].

4.3. Role of the Duration of Exercise on BDNF and Cognitive

In addition to exercise intensity, duration is also known to affect various effects of exercise [32]. Duvivier et al. [33]. At least 30 minutes of exercise thrice a week was associated with improved health status [34]. Therefore, duration and intensity are the main factors that enhance hypothalamic responses. This increase is related to memory with a shorter duration, with a duration of 3 minutes for older people whose cycling exercises can increase maximum fitness, which causes maximum cognitive performance [35]. A longer duration of 30 minutes on a treadmill can improve the accuracy of exercise intensity so that cognitive function and memory increase [33], likewise for the duration of 45 minutes to 100 minutes [12,23]. Improved cognitive function memory and visual-spatial skills with a shorter duration, long-term spatial memory, and working memory on exercises prove that exercise duration affects memory performance [14]. However, in the 2015 study by Chien Heng Chu. et al., cycling at moderate intensity without the duration of exercise can also improve cognitive function [19]. So Matthew T. Schmolesky. et al. 2013 suggested that no factor (intensity or duration) affects the increase in BDNF from exercise [20].

4.4. Effects of Exercise on Age and Gender on BDNF and Cognitive

Lifelong structural and functional changes to environmental reactions and individual experiences depend on neural plasticity and brain capacity. However, with age, the brain's ability to adapt to the environment decreases gradually, leading to a decline in brain function. Older adults react less quickly and accurately than younger adults on tests of perceptual speed, memory, decision-making, and multitasking abilities, leading to cognitive decline [34]. Aging populations that experience decreased brain and cognitive function due to normal aging are associated with approximately 15% to 25% brain volume atrophy and degradation of cognitive processes, including memory, reasoning, and information processing speed [35].

Physical exercise causes changes in brain health and cognitive function with cellular and structural changes in animal brains that, including increased neurogenesis and synaptogenesis, dendritic remodeling, and synaptic plasticity, are the main biological changes elicited in the elderly [36].

The effect of exercise on cognitive performance in younger people shows positive changes in cognitive performance with low to moderate impacts [37]. Whereas in adults and the elderly, acute exercise training improves cognitive performance, as well as the elderly living in the community, and physical and recreational exercise, can significantly improve cognitive function and quality of life [24].

Mechanisms of exercise improve brain function, including cognitive function influenced by a neurotrophic factor (BDNF), which facilitates exercise-induced neurogenesis [38]. BDNF is involved in increasing the survival of progenitor cells that have the potential to differentiate into nerve cells or glial cells and directly enhance neuronal cell differentiation. Various studies have found that BDNF expression increases with regular exercise and acute exercise [2,32].

Acute aerobic exercise induction effectively increases peripheral BDNF concentration [25]. Regular physical activity and exercise are methods for "healthy aging" [34]. It has been shown that long-term regular exercise promotes healthy body composition [14]. Regular exercise effectively improves cognitive function in older women [36]. Still, in Louis Nurfagah Forti et al., 2015, there was no difference in BDNF levels of high and low-intensity exercise in women and no change in serum BDNF in women. Elderly at rest and physical exercise [38].

Interestingly, the elderly participants had lower serum BDNF concentrations than healthy young individuals, but at the same time, their plasma BDNF levels were comparable. This is at least partly related to the decline in platelet count due to aging. However, in a study by Natalie Frost B. Psych et al. (2021) with six months of high-intensity aerobic exercise, there was no improvement in executive function in older adults; this may be due to individual differences in exercise-induced changes in cardiorespiratory fitness associated with changes in cardiorespiratory fitness, working memory [39].

The level of BDNF circulating in the blood circulation is influenced by age and gender. BDNF concentrations difference in age, and neuronal loss in the elderly is associated with low peripheral BDNF levels [40]. In addition, Chang (2012) found sex differences in platelet BDNF but not plasma BDNF levels. BDNF concentrations were higher in women than in men [40]. Animal studies have shown that BDNF is positively modulated by estrogen. Compared to humans, it could be assumed that the decrease in estrogen levels in women due to menopause could be promoted to decrease BDNF production [42].

Meanwhile, there may be a range of circulating basal BDNF which vary from male to female. Physical exercise may impact restoring or stabilizing BDNF levels. Although not statistically significant, women tend to show higher baseline BDNF levels than men. Interestingly, Golden et al. 2010 observed considerably higher levels of BDNF in female participants than in male participants [43]. In addition, a significant correlation of BDNF with bioavailable testosterone and sex hormone-binding globulin was reported. Men with higher levels of BDNF tend to have lower sex hormone-binding globulin, and aging is associated with decreased bioavailable testosterone and increased sex hormone-binding globulin. Older men with low resistance exercise may increase plasma BDNF [44].

BDNF, produced in the CNS, can be detected in almost every part of the brain [45]. BDNF in the female hippocampus was higher than in males. Carta et al (2021) also demonstrated lower BDNF levels in the male CA3 region hippocampus. However, in the dentate gyrus dorsal hippocampus, male rats had more BDNF than females [22]. In contrast to BDNF, male rats in the hippocampus were higher than females. In humans, there was no significant difference in hippocampal BDNF between men and women, but women had increased BDNF in the prefrontal context [46].

5. Conclusion

This review provides evidence regarding the role of exercise type, intensity, and duration in increasing BDNF concentration and cognitive function in adults and the elderly. As for the kind of exercise, aerobic exercise causes the circulation of blood flow to the lungs and heart to increase so that the blood pump from the heart to the brain increases. As for the intensity of exercise, exercise with moderate to high intensity increases VO_2max, hemodynamics, cellular metabolism, oxidation reactions, memory formation, and mood regulation. For exercise duration, longer exercise duration affects the hypothalamus, thereby improving health status. All of these mechanisms harmonize the effect of exercise on synaptic plasticity in response to an increase in BDNF that will affect cognition.

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