

The neuroprotective effects of exercise on memory

Fitranto Arjadi*¹

¹Anatomy Department, Medical Faculty, Jenderal Soedirman University, dr Gumbreg Street No 1 Purwokerto 53112, Central Java, Indonesia

EDITORIAL

ARTICLE INFO

*Corresponding author:

fitranto.arjadi@unsoed.ac.id

DOI: 10.20885/JKKI.Vol14.Iss3.art1

Copyright ©2023 Authors.

Memory is mediated by a complex network that comprises the ventral and dorsal regions of the striatum, cingulate cortex, mesolimbic, and front parietal cortex, which is a crucial component of cognitive flexibility. The brain's ability to retain and store learned information, as well as to perform appropriate behavior based on lifelong experience, is known as memory. Any memory retrieval deficiencies could have a significant influence on a person's everyday activities and health.¹ Some of the leading causes of memory impairment include neurodegenerative diseases (Parkinson's disease and dementia), strokes, brain aneurysms, traumatic brain injuries, primitive or metastatic neoplasms, and infectious disorders such as encephalitis are examples of clinical situations, and other conditions (drug abuse like marijuana and benzodiazepines, antiepileptic medications, opioids, tricyclic antidepressants, heavy smoking, excessive stress, sleep deprivation, and vitamin B12 deficiency).² A number of behavioral and non-behavioral techniques have been put forth to improve memory tests. The elaborative rehearsal and cognitive training are the two primary components of behavioral methods or cognitive training, which concentrates on associating newly learned material with previously stored knowledge and analyzing newly learned material to make it memorable, and the maintenance rehearsal, which aids memory processing by presenting repetitive stimuli. Numerous behavioral strategies have been suggested, some of which include exercise training.²

The World Health Organization (WHO) defines exercise training as planned, systematic, and repetitive physical activity that preserves cognitive function in the brain, especially working memory. Exercise-induced memory improvement is mediated by both indirect and direct supramolecular and molecular pathways.³ The term "supramolecular level" describes modifications to an organ's structure or physiological functions, such as increased blood flow, increased gray matter integrity, or increased hippocampus volume.⁴ The hippocampus, a region crucial to memory and learning, has improved cerebral circulation when people engage in regular physical activity.⁵ During contraction, the skeletal muscles release lactate, which is absorbed by the brain and causes the primary motor cortex to become excitable. It also increases the density of cerebellar cortex vessels and brain vascular endothelial growth factor.⁶ Enough blood flow to the brain allows waste products like amyloid-beta and aberrant proteins in the hippocampus and frontal cortex to be eliminated, protecting brain tissue and enhancing memory acquisition and retrieval.⁷

Physical activity and cardiorespiratory fitness levels that are higher increase the volume and integrity of brain structures, especially the hippocampus and the entorhinal cortex, and improve memory performance.⁸ Intense exercise training also produces lactate, which increases the proliferation of glial cells and neurons, especially in the hippocampus;⁹ it also induces the expression of brain-derived neurotrophic factor (BDNF) in the hippocampus, which in turn stimulates

neurogenesis.¹⁰ Skeletal muscle contraction results in the release of proteins into the bloodstream known as myokines.² These proteins increase neurotrophic factors, including insulin-like growth factor (IGF-1), BDNF, and irisin, which are important for long-term memory and hippocampal plasticity.¹¹

Serum BDNF levels are raised by exercise training in tandem with improvements in memory.¹² According to cellular and molecular mechanisms, lactate produced by contraction of skeletal muscles, crosses the blood-brain barrier, causes BDNF expression, and plays a significant role in cognition by promoting synaptic regeneration, long-term potentiation, protein phosphorylation, and memory enhancement.¹³ Considering the significance of BDNF levels for memory and neuroplasticity, these findings support the idea that physical activity ought to be incorporated into rehabilitation regimens for various neurodegenerative conditions. Exercise training also results in an increase in IGF-1 levels (centrally and peripherally), increases the expression of BDNF and synaptic plasticity markers in the hippocampus, including postsynaptic density protein-95 and synaptophysin, and has positive effects on both aversive and spatial memories.¹⁴

Exercise training has been demonstrated to raise circulating catecholamine levels, which improves intermediate and long-term memory retention.¹⁵ Noradrenaline levels raised by exercise have a potentiating effect on memory and learning. Regular aerobic exercise and physical activity increase levels of endocannabinoid (EC), a system of biological lipids that basically modulates the endocrine, nervous, and immune systems.¹⁶ This has been linked to long-term positive effects on neural plasticity and memory.¹⁷ After exercise, contracted skeletal muscles increase the release of several paracrine factors known as myokines, such as irisin, which is linked to BDNF secretion and improves memory retrieval.¹⁸ Both short and long-term epigenetic regulations are induced by acute and regular exercise training, which results in the creation of a "functional genome" and adaptation throughout an individual's active life span. For instance, DNA methylation, histone acetylation, and up- and down-regulation of microRNA may all play a role in the memory-boosting benefits of exercise training.¹⁹ Recently, following aerobic exercise, plasticity and memory consolidation, storage, and retrieval in senescence-accelerated mice have been linked to an increase in BDNF histone acetylation and the expression of the immediate early genes of c-fos and Arc.²⁰

Exercise improves neuronal reserve by increasing BDNF expression, which promotes synaptic plasticity and neurogenesis, lowering oxidative stress and inflammation, and improves peripheral and cerebral blood flow. This, in turn, angiogenic factors are stimulated, resulting in favorable changes in the morphology and structure of the brain vasculature. It's still unclear how variables for exercise, like duration, length, frequency, and intensity, affect cognitive health, and how much exercise is necessary to see benefits is also unknown.²

The conclusion is that the neuroprotective mechanisms of exercise training may be related to the finding that regular moderate aerobic exercise is associated with improved neurocognitive performance. Regular exercise improves brain circulation, mitochondrial biogenesis, neurotrophic factors, and the release of numerous signaling molecules, including myokines and adipokines. At the moment, it appears that irisin/BDNF signaling is the primary mechanism underlying the facilitative effects of exercise on memory and learning.

LIST OF ABBREVIATIONS

BDNF: brain-derived neurotropic factor, IGF-1: insulin-like growth factor-1, EC: endocannabinoid, DNA: Deoxyribonucleid acid, RNA: Ribonucleid acid, WHO: World Health Organization

REFERENCES

1. Babaei PA, Azari HB. Exercise training improves memory performance in older adults: A narrative review of evidence and possible mechanisms. *Front Hum Neurosci.* 2022; 15(771553).
2. Arida RM, Teixeira-Machado A. The contribution of physical exercise to brain resilience. *Front Behav Neurosci.* 2021;14:1-18.
3. WHO. Risk reduction of cognitive decline and dementia. WHO Guidelines.(ed.) ISBN-13: 978-92-4-155054-3
4. Guiney H, Machado L. Benefits of regular aerobic exercise for executive functioning in healthy populations. *Psychon Bull Rev.* 2013; 20:73-86.
5. Mandolesi L, Gelfo F, Serra L, Montuori S, Polverino A, Curcio G et al. Environmental factors promoting neural plasticity: Insights from animal and human studies. *Neural Plast.* 2017;7219461.
6. Morland C, Andersson KA, Haugen ØP, Hadzic A, Kleppa L, Gille A, et al. Exercise induces cerebral

- VEGF and angiogenesis via the lactate receptor HCAR1. *Nat Commun.* 2017;8:15557.
7. Li B, Liang F, Ding X, Yan Q, Zhao Y, Zhang X, et al. Interval and continuous exercise overcome memory deficits related to β -amyloid accumulation through modulating mitochondrial dynamics. *Behav Brain Res.* 2019;376:112171.
 8. Clark IA, Callaghan MF, Weiskopf N, Maguire EA. The relationship between hippocampal-dependent task performance and hippocampal gray matter myelination and iron content. *Brain Neurosci Adv.* 2021;5(23982128211011924).
 9. Elahi M, Motoi Y, Matsumoto SE, Hasan Z, Ishiguro K, Hattori N. Short-term treadmill exercise increased tau insolubility and neuroinflammation in tauopathy model mice. *Neurosci Lett.* 2016; 610:207–212
 10. El Hayek L, Khalifeh M, Zibara V, Abi Assaad R, Emmanuel NK, Karnib N, et al. Lactate mediates the effects of exercise on learning and memory through SIRT1-dependent activation of hippocampal brain-derived neurotrophic factor (BDNF). *J Neurosci.* 2019;39:2369–2382.
 11. Duzel E, van Praag H, Sendtner M. Can physical exercise in old age improve memory and hippocampal function? *Brain.* 2016; 139, 662–673.
 12. Marinus N, Hansen D, Feys P, Meesen R, Timmermans A, Spildooren J. The impact of different types of exercise training on peripheral blood brain-derived neurotrophic factor concentrations in older adults: a meta-analysis. *Sports Med.* 2019;49:1529–1546.
 13. Babaei P. NMDA and AMPA receptors dysregulation in Alzheimer's disease. *Eur J Pharmacol.* 2021;2921:908,174310.
 14. Segabinazi E, Gasperini NF, Faustino AM, Centeno R, Dos Santos A, Almeida WD, et al. Comparative overview of the effects of aerobic and resistance exercise on anxiety-like behavior, cognitive flexibility, and hippocampal synaptic plasticity parameters in healthy rats. *Braz J Med Biol Res.* 2019;53:e9816.
 15. Winter B, Breitenstein C, Mooren FC, Voelker K, Fobker ML, Lechtermann A. High impact running improves learning. *Neurobiol Learn Mem.* 2007;87(4), 597–609.
 16. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: Signaling and function in the central nervous system. *Int J Mol Sci.* 2018;19:833.
 17. Meyer JD, Crombie KM, Cook DB, Hillard CJ, Koltyn KF. Serum endocannabinoid and mood changes after exercise in major depressive disorder. *Med Sci Sports Exerc.* 2019;51:1909–1917.
 18. Babaei P, Mojtavavi K, Kouhestani S. The Effect of intrahippocampal injection of insulin-like growth factor-1 on morphine-induced amnesia in wistar rats. *J Kerman Univ Med Sci.* 2017;26:185–191.
 19. Grazioli E, Dimauro I, Mercatelli N, Wang G, Pitsiladis Y, Di Luigi L, et al. Physical activity in the prevention of human diseases: Role of epigenetic modifications. *BMC Genomics.* 2017;18(Suppl.):802–808.
 20. Maejima H, Kitahara M, Takamatsu Y, Mani H, Inoue T. Effects of exercise and pharmacological inhibition of histone deacetylases (HDACs) on epigenetic regulations and gene expressions crucial for neuronal plasticity in the motor cortex. *Brain Res.* 2021;1751(147191).