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Posted Date: 5 September 2023

doi: 10.20944/preprints202309.0210.v1

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Review

Mechanisms of the Beneficial Effects of Exercise on Brain-Derived Neurotrophic Factor Expression in Alzheimer's Disease

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Abstract: Brain-derived neurotrophic factor (BDNF) is a key molecule in promoting neurogenesis, dendritic and synaptic health, and neuronal survival, plasticity, and excitability, all of which are disrupted in neurological and cognitive disorders such as Alzheimer's disease (AD). Extracellular aggregates of amyloid-β (Aβ) in the form of plaques and intracellular aggregates of hyperphosphorylated tau protein have been identified as major pathological insults in AD brain, along with immune dysfunction, oxidative stress, and other toxic stressors. Although aggregated Aβ and tau lead to decreased brain BDNF expression, early losses in BDNF prior to plaque and tangle formation may be due to other insults such as oxidative stress and contribute to early synaptic dysfunction. Physical exercise, on the other hand, protects synaptic and neuronal structure and function, with increased BDNF as a major mediator of exercise-induced enhancements in cognitive function. Here, we review recent literature on mechanisms behind exercise induced BDNF upregulation and its effects on improving learning and memory and on Alzheimer's disease pathology. Mechanisms include elevations in peripheral BDNF-inducing hormones such as osteocalcin, FNDC5/irisin, and lactate. The fundamental mechanisms of how exercise impacts BDNF and cognition are unclear but are a prerequisite to developing new biomarkers and therapies to delay or prevent cognitive decline.

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1. Brain-derived neurotrophic factor and Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder that is clinically characterized by progressive memory loss and cognitive decline and that shows an increasing incidence rate in aging individuals [1]. Of the several pathological hallmarks of AD, extracellular accumulation of amyloid-β (Aβ) aggregates and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles are the best-known [2]. Aβ1–42 (Aβ42), the primary component of plaques found in AD brain, is formed by alternative proteolytic cleavage of the amyloid precursor protein (APP) by the proteases β- (BACE1) and γ-secretases, forming a pathological variant of the protein that is soluble and has a tendency to oligomerize [3–5]. While extracellular aggregates disrupt synaptic function, intracellular levels of Aβ42 increase in Down syndrome [6] and AD [7,8] and have been linked to apoptotic cell death via a caspase cascade [9,10].

One of the ways that neurotoxic Aβ42 exerts its neurodegenerative effects is by decreasing brain-derived neurotrophic factor (BDNF) levels and disrupting one of BDNF's major transcriptional regulators and mediators, cyclic adenosine monophosphate response element binding protein (CREB) [11]. BDNF has a fundamental role in promoting neuronal survival, neurogenesis, maintenance and growth of dendrites, synaptic transmission, plasticity, and excitability [11–15]. Thus, it plays a significant role in hippocampal memory formation. BDNF is involved in the

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occurrence and maintenance of both early-phase and late-phase LTP, which correspond to short-term and long-term hippocampal memory, respectively [16].

Severity of cognitive impairments in AD is inversely correlated with the level of BDNF in the brain [17,18]. Significant downregulation of BDNF mRNA, resulting in a 50% reduction of available BDNF protein [17,19], occurs in AD. CREB, a transcriptional regulator of BDNF and a downstream mediator of its activity [20–23], is also reduced in AD. In glutamate stimulated hippocampal neurons treated with toxic oligomeric Aβ42, there is a significant decrease in activity of PKA, which phosphorylates CREB [24]. In the absence of cell stimulation, on the other hand, Aβ42 downregulates CREB mRNA levels without affecting its basal phosphorylation levels [25,26]. Therefore, Aβ42 may impair cognitive function by reducing signaling through a BDNF/CREB autoregulatory loop, downregulating BDNF and CREB expression as well as reducing CREB phosphorylation.

Pathological tau also downregulates BDNF at the transcriptional level [27,28]. Although the precise molecular pathway by which this occurs is not well understood, hyperphosphorylated tau may reduce BDNF expression by inhibiting PKA and CREB phosphorylation [29] or other transcription factors.

2. Physical Exercise and Brain Health

The benefits of exercise on brain structure and function have been the topic of study for decades. Improvements in synaptic plasticity, structure, and strength with physical exercise training are well-established in the literature [30]. In addition to enhanced efficiency in neural processing [31], prefrontal cortex and hippocampus are larger in adults with higher aerobic fitness [32]. Many studies in animals have shown improved hippocampal-dependent cognitive tasks following a period of exercise participation [30,33–35].

Human clinical trials on the effects of exercise on cognition have produced variable results. In addition to increases in functional ability, a 6-month aerobic exercise protocol in older adults with AD or mild cognitive impairment (MCI) showed improved memory performance and reduced hippocampal atrophy [36]. Similarly, a 6-month mind-body exercise protocol in the form of Baduanjin training showed significant improvements in cognitive function and increased hippocampal gray matter volume in individuals with MCI [37]. Furthermore, 6-months of aerobic exercise yielded cognitive enhancement, increased frontoparietal network connectivity, and reduced brain atrophy in patients with Parkinson's disease (PD) [38]. While the studies above showed slowing of disease progression and reduced brain atrophy in AD, MCI, and PD patients with exercise, another exercise study did not observe any changes in age-related brain atrophy in healthy older adult brain, despite improvements in cognition [39]. Furthermore, the above results are contradicted by several studies [40–42] and meta-analyses [43] that found no significant improvements in executive function, memory, or information processing with exercise training in older adults with subjective cognitive decline, MCI, or dementia, or only reported mild improvements in cognition [44] or improvements in single domains such as executive function [45]. Contradictions in clinical trial results may be explained by differences in protocols such as exercise duration, intensity (low-, moderate-, high-intensity exercise), and type (aerobic, resistance, strength exercise). Nevertheless, recent meta-analyses suggest that physical exercise, particularly aerobic exercise, improves cognition in those with MCI and dementia [46], possibly by increasing neuroprotective factors such as BDNF [47,48].

Mechanisms behind exercise-induced improvements in neuronal health, synaptic function, neurogenesis, and cognitive function are currently under investigation. One compelling hypothesis is the role of exercise in regulating growth factors in both central and peripheral tissues. BDNF is a leading candidate for study in this field due to its extensive role in promoting neuronal survival, neurogenesis, synaptic plasticity, and cognitive function [15,49–53]. Voluntary wheel running in rats results in significant increases in BDNF mRNA in the hippocampus, specifically in the dentate gyrus (DG) and Ammon's horn areas 1 and 4 (CA1, CA4) [33], CA3, and cerebral cortex [54,55]. Increases in BDNF mRNA are also detected in the spinal cord and skeletal muscle following treadmill training in rats [56].

Measuring BDNF changes in the brain of human participants is not currently feasible; therefore, investigators use BDNF levels in serum or plasma as a proxy. Serum and plasma BDNF levels rise as a consequence of acute or regular exercise [47,57–61]. Peripheral BDNF found in the bloodstream is derived mainly from vascular endothelial cells, much of which is bound by platelets, where it constitutes a major source of BDNF in serum [62,63]. However, whether free BDNF can cross the blood-brain barrier bidirectionally, and whether peripheral BDNF levels reflect BDNF levels in the brain, is controversial. While some studies have shown that brain-derived BDNF can cross the blood-brain barrier and enter the circulation [64,65], other studies demonstrate that circulating BDNF does not enter the brain [66]. Several studies have reported a positive correlation between central and peripheral BDNF levels in animals, suggesting that serum and plasma BDNF levels may reflect brain BDNF levels. A positive correlation was found between hippocampal BDNF levels and plasma BDNF levels in pigs and between BDNF levels in hippocampus and prefrontal cortex and BDNF levels in whole blood and serum of rats [67–69]. Interestingly, because mouse platelets do not contain BDNF, this neurotrophin has been undetectable in mouse blood [67] until the recent advent of a highly sensitive BDNF ELISA [70]. Consistent with the animal work, human studies of serum or plasma BDNF suggest that exercise-induced increases in peripheral BDNF levels reflect brain BDNF levels. There is evidence of increased serum BDNF levels in younger [59,71] and older adults [57,72–75] following exercise training. The increased BDNF levels are correlated with higher memory scores as well as increased hippocampal volume post-exercise training, further supporting the usefulness of peripheral measures for judging central effects [71,73,76,77].

3. Mechanisms of BDNF upregulation with exercise

3.1. Osteocalcin, a bone-derived hormone, plays a role in learning and memory via BDNF

Physical exercise has a multifaceted effect on the body. A diverse array of myokines, cytokines, and peptides are released in response to exercise. Many of these molecules play an essential role in regulating energy metabolism. Osteocalcin, an osteoclast-specific hormone, functions in an array of physiological processes such as glucose homeostasis and exercise capacity as well as brain development and cognition [78]. One session of high-intensity exercise produces a significant increase in serum levels of uncarboxylated osteocalcin (a bioactive form of osteocalcin) [59,79,80]. Release of uncarboxylated osteocalcin from bone is induced by interleukin 6 (IL-6), an anti-inflammatory myokine secreted in response to exercise [81]. IL-6 signalling induces osteoclast differentiation and promotes uncarboxylated osteocalcin release. This is evident in IL-6 deficient mice that do not exhibit an increase in osteocalcin levels in response to exercise [81].

Several studies have suggested that osteocalcin is necessary for establishing spatial learning and hippocampal-dependent memory. Osteocalcin knockout mice have impaired spatial learning and hippocampal-dependent memory as well as increased anxiety-like behaviour, as evident by the novel object recognition test, Morris water maze, light/dark transition test, elevated plus maze, and open-field test [82]. Moreover, osteocalcin knockout mice have smaller brains than wildtype mice, with particular deficits seen in the dentate gyrus and corpus callosum [83]. Injecting plasma from young mice into older mice improved age-related cognitive impairment [84], but only when the plasma contained osteocalcin [85]. Plasma from osteocalcin knockout mice improved hippocampal-dependent memory and reduced anxiety-like behaviour in aged wildtype mice only when supplemented with uncarboxylated osteocalcin.

Osteocalcin's effects on cognition may be mediated by BDNF. Khrimian et al. [85] identified an orphan class C G-protein coupled receptor (GPCR), Gpr158, as the receptor through which osteocalcin mediates its cognitive effects on the brain. In a signalling pathway assay, osteocalcin was found in a complex with Gpr158/Gαq and increased the production of inositol 1,4,5-triphosphate (IP3) in wildtype hippocampal neurons. IP3 is a second messenger that facilitates the exocrine secretion of various molecules, including BDNF, and may also mediate increases in BDNF expression [86]. Binding of IP3 to its receptor causes a surge of calcium into the cytoplasm from intracellular calcium stores [86], which leads to the activation of a Ca2+/calmodulin-dependent kinase (CaMK)

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pathway that upregulates CREB [23,87]. The role of osteocalcin/Gpr158 signalling in BDNF expression is evident in Gpr158-knockout mice, where BDNF expression is significantly reduced; and while osteocalcin treatment does not alter BDNF expression in these mice, it significantly increases BDNF expression in wildtype mice expressing Gpr158 [85]. This confirms that osteocalcin increases BDNF expression in the brain via Gpr158 receptor.

Another important component of osteocalcin/Gpr158 signalling is the histone-binding protein, RbAp48 [88]. RbAp48 can be found in a complex with CREB binding protein (CBP) and enhances its acetyl transferase activity [89], which is critical for long-term memory formation and synaptic plasticity [90–92]. Recently, RbAp48 was also found to be involved in transcriptional activation of Gpr158 by binding to its promoter, controlling its expression in the hippocampus. In turn, osteocalcin/Gpr158 signalling modulates RbAp48 expression, since knocking down Gpr158 leads to a reduction in RbAp48 protein levels and memory performance, while activation of the osteocalcin/Gpr158 pathway upregulates RbAp48 expression and rescues age-related memory loss [88].

Current literature demonstrates that physical exercise increases uncarboxylated osteocalcin levels, which act through Gpr158 to improve hippocampal memory. Evidence suggests that osteocalcin's effects are mediated by BDNF. Further questions include whether osteocalcin improves cognitive function in the absence of BDNF signalling, and the role of RbAp48 in osteocalcin induced BDNF upregulation.

3.2. FNDC5/irisin increases BDNF levels in the hippocampus and supports learning and memory

Exercise induces the expression of many distinct types of proteins, including several active myokines from muscle. The muscle-derived factor, irisin, is released into the circulation immediately after exercise [93]. Irisin is released by proteolytic cleavage of the extracellular portion of fibronectin type III domain containing 5 (FNDC5), a transmembrane glycoprotein [93]. Irisin functions in energy expenditure, metabolism, and insulin resistance. In addition to its roles in metabolism, FNDC5/irisin is also expressed in the hippocampus and cortex [94,95]. Irisin influences neuronal development, since knocking down FNDC5 in mouse embryonic stem cells significantly reduces their neural differentiation [96]. FNDC5/irisin is reduced in AD and in AD mouse models, leading to impaired long-term potentiation and poor memory performance. Conversely, overexpression of FNDC5 in an AD mouse model rescues memory and synaptic plasticity [94]. Furthermore, exercise prevents reductions in FNDC5/irisin, BDNF, and memory performance in mouse models of AD.

Peripheral delivery of irisin increases central levels of irisin in FNDC5 knockout mice and in mouse models of AD and rescues cognitive impairment in these mice [94,97]. Interestingly, inhibition of either peripheral or central FNDC5/irisin leads to impaired long-term potentiation and poor memory performance in exercised mice [94].

Neuroprotective effects of irisin are mediated by increases in BDNF expression. Exercise-induced expression of FNDC5 in hippocampus stimulates expression of BDNF in the brain, but not in brain areas where FNDC5 is not expressed [95]. Expression of FNDC5 in primary cortical neurons increases expression of BDNF and mediators of BDNF involved in hippocampal function including Npas4, c-Fos, and Arc [95]. Treatment of mouse hippocampal and human cortical slices with recombinant irisin stimulates the cAMP/PKA/CREB pathway [94], which is known to increase BDNF mRNA and protein levels [11]. Conversely, BDNF expression is reduced in primary cortical neurons treated with FNDC5 shRNA and in peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α knockout mice, a key regulator of FNDC5 gene expression [95,98]. Mice subjected to treadmill running exhibit increases in hippocampal PGC1α and FNDC5 protein levels and plasma irisin levels which correlate with increased BDNF mRNA levels and cell proliferation in the hippocampus. These increases are blocked when the mice are treated peripherally with an irisin-neutralizing antibody [99]. Lastly, peripheral expression of FNDC5 in the liver via adenoviral vectors increases BDNF expression in the brain, suggesting that peripheral irisin or a metabolite may cross the blood-brain barrier and induce BDNF expression [95]. Whether the main effect of exercise-induced irisin on cognition is via peripheral or central irisin is not fully understood. The mechanism

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and transporters have not been identified. Regardless, the above results confirm that exercise-induced irisin has a direct effect on BDNF expression levels in the hippocampus and plays a critical role in spatial learning and memory.

3.3. Lactate release from muscle following exercise induces BDNF in hippocampus and promotes learning and long-term memory formation

An important byproduct of exercise is lactate released by exercising muscles, which is commonly known to cause a burning sensation during intense exercise. When oxygen becomes limiting in muscle cells, pyruvate is reduced in a reaction catalyzed by lactate dehydrogenase, producing lactic acid. During this process, nicotinamide adenine dinucleotide (NAD+) is regenerated, allowing glycolysis to continue to generate adenosine triphosphate in the absence of oxygen. For many years, lactate was overlooked as only a byproduct. However, recent evidence demonstrates the beneficial role of lactate in the body and the brain.

Peripheral lactate can be transported across the blood-brain barrier via monocarboxylate transporter 1 (MCT1) [100,101], however lactate in the brain is predominantly generated from glucose metabolism in astrocytes [102,103]. During excitatory neurotransmission, lactate provided to neurons by astrocytes can be used as an energy source by conversion to pyruvate which enters the citric acid cycle [104]. Interestingly, it has been suggested that astrocyte-neuron lactate transport is necessary for long-term memory formation [102,105] and can regulate memory processing [106]. Knocking down lactate transporters MCT1 and MCT4 (expressed in astrocytes and oligodendrocytes) in the rat hippocampus disrupts long-term but not short-term memory. Exogenous administration of L-lactate, but not glucose, rescues memory retention in these MCT knockdown rats [102]. Interestingly, knocking down MCT2 (expressed in neurons) also disrupts long-term memory formation, but L-lactate and glucose administration fail to rescue memory retention in these rats. This confirms that lactate transport to neurons through MCT2 is necessary for long-term memory formation.

There is a positive correlation between peripheral circulating lactate concentrations and BDNF levels in serum or plasma [107]. Two potential mechanisms through which lactate might increase BDNF expression are by potentiating N-methyl-D-aspartate receptor (NMDAR) signalling [108] and via activating the PGC1α/FNDC5/BDNF pathway [109]. Yang et al. (2014) showed that L-lactate induces the expression of plasticity-related genes such as Arc, Zif268, c-Fos, and BDNF in neurons in vitro and in vivo. Lactate may increase BDNF expression by activating NMDA receptors and extracellular signal-regulated kinase 1/2 (Erk1/2). When treated with an NMDAR antagonist, increases in Arc and Zif268 mRNA and protein levels [108] and BDNF mRNA levels [110] were blocked. Inhibiting Erk1/2 reduced L-lactate-stimulation of Arc and Zif268 mRNA and protein levels, although the effect of blocking Erk1/2 on BDNF and c-fos expression was not reported in this study. However, it is known that Erk1/2 can activate CREB and upregulate BDNF expression as a result [111], and that BDNF can activate CREB and Erk1/2 [14]. Together, these results confirm that lactate induces an increase in plasticity-related genes via the Erk1/2 pathway, which is downstream of NMDAR signalling [112]. These effects were not observed with D-lactate (its nonmetabolized enantiomer), L-pyruvate, or D-glucose, making them selective to L-lactate.

El Hayek et al. [109] demonstrated that hippocampal increases in BDNF expression and signalling in exercising mice are lactate dependent. Intraperitoneal injection of MCT1/2 inhibitor abolished the increase in BDNF expression and signalling in exercising mice, showing that lactate transport to neurons via MCT1/2 is necessary for exercise-induced BDNF expression and signalling. Moreover, lactate significantly increased BDNF expression in hippocampal and cortical neurons in culture. Lactate-injected mice exhibited better performance than control mice in Morris Water Maze tests of spatial learning and memory, but not when cotreated with the TRK inhibitor CEP701. Thus, these results indicate that lactate increases BDNF levels and improves learning and memory. Voluntary exercise or lactate injections increased hippocampal PGC1α and FNDC5 protein levels, suggesting that lactate-induced BDNF expression may occur through the PGC1α/FNDC5/BDNF pathway. Furthermore, both voluntary exercise and intraperitoneal lactate injections led to an increase in hippocampal levels of silent information regulator 1 (SIRT1), which is a NAD+-dependent deacetylase involved in gene regulation [104]. Knocking down SIRT1 abolished lactate induced BDNF expression in the hippocampus. Moreover, cotreatment with lactate and an inhibitor of SIRT1, sirtinol, blocked increases in PGC1α protein levels. Therefore, lactate leads to hippocampal expression of BDNF through a SIRT1-dependent induction of PGC1α and FNDC5. As mentioned previously, the PGC1α/FNDC5/BDNF pathway activates the cAMP/PKA/CREB pathway, which upregulates BDNF expression and regulates learning and memory formation.

4. Exercise-induced BDNF reduces APP toxicity by altering its processing

Inactivity is a risk factor for AD [113–117]. Of note are the higher levels of circulating Aβ protein in sedentary individuals compared to individuals who exercise [116–118] and the correlation between increased circulating Aβ and increased risk of developing AD and MCI [3]. Both in vitro and in vivo studies show that BDNF reduces amyloidogenic Aβ and decreases its neurotoxic effects [119–121], and it may mediate this effect by altering APP processing. Therefore, scientists investigated a possible relationship between BDNF and some of the enzymes involved in APP processing: α-, β-, γ-, and δ-secretase. α-secretase is involved in non-amyloidogenic cleavage of APP, while β- and γ-secretase promote the production of toxic Aβ [122]. δ-secretase, also known as asparagine endopeptidase (AEP), is a cysteine proteinase activated during aging that cleaves APP. δ-secretase cleavage generates an APP fragment that may be the preferred substrate for β-secretase, thereby enhancing β-secretase cleavage of APP and the production of Aβ [123]. In the absence of BDNF signalling, δ-secretase expression is increased via C/EBPβ upregulation [121], while increased BDNF signalling increases Akt phosphorylation of δ-secretase, which inhibits its activity [124].

In parallel, β-site amyloid precursor protein cleaving enzyme 1 (BACE1 or β-secretase) is an important enzyme responsible for cleaving APP and releasing soluble Aβ peptide (i.e., amyloidogenic pathway). There is evidence that both chronic and acute exercise in mice lead to a reduction of BACE1 content, consequently decreasing Aβ accumulation and improving recognition memory [125,126]. Treatment of brain tissue with BDNF yielded a significant reduction in BACE1 activity [125], while BDNF deprivation yielded increased BACE1 protein levels [121]. These results suggest another possible mechanism by which BDNF reduces amyloidogenic APP processing, although more studies are needed to elucidate the mechanism of BDNF-induced BACE1 downregulation.

A third possible mechanism by which exercise-induced BDNF reduces Aβ production is by enhancing ADAM10 activity. ADAM10 is the main active component of α-secretase [127]. As expected, treatment of RA-differentiated human SHSY5Y neural cells with ADAM10 inhibitor significantly increased the production of Aβ. BDNF treatment of SHSY5Y cells significantly reduced Aβ production. However, when cotreated with BDNF and ADAM10 inhibitor, Aβ levels were still significantly higher than controls [128]. These results suggest that a possible mechanism through which BDNF reduces Aβ toxicity is by enhancing ADAM10 activity. Interestingly, BDNF does not alter ADAM10 protein levels [126,128] but enhances its activity by altering its distribution in the cell toward intracellular accumulation, where regulated α-secretase activity occurs, rather than on the cell surface [128]. Together, these results suggest that possible mechanisms by which exercise-induced upregulation of BDNF reduces AD pathology include increasing α-secretase activity and decreasing β- and δ-secretase levels, shifting the balance of APP processing towards the nonamyloidogenic pathway and reducing Aβ toxicity in the brain.

5. Conclusions

BDNF is a critical molecule for neuronal health and survival, neurogenesis, synaptic plasticity, neuronal excitability, and learning and memory. BDNF deficiency is correlated with mild cognitive impairment, Alzheimer's disease, Parkinson's disease, and other neurodegenerative disorders. Physical exercise has produced promising results in improving neurodegenerative- and age-related learning and memory deficits, and its effects are at least partially mediated by upregulating BDNF levels. Here, we reviewed several molecules released in response to exercise that facilitate BDNF upregulation. Uncarboxylated osteocalcin release, induced by IL-6, increases BDNF expression.

Osteocalcin-induced upregulation of BDNF is mediated through Gpr158 signalling, which activates a pathway involving IP3/CaMK/CREB. Another exercise-induced molecule is FNDC5/irisin, which is expressed in the brain and is released from muscle post-exercise. Peripheral and central irisin both contribute to learning and memory by stimulating the cAMP/PKA/CREB/BDNF pathway. Future studies should investigate the transporters and mechanisms by which irisin may cross the blood-brain barrier. Moreover, it is important to consider whether peripheral or central irisin is responsible for its effects on cognition post-exercise. Similarly, lactate is released from muscle following exercise and is also produced by astrocytes in the brain. It may be upregulating BDNF expression in the brain by activating NMDA receptors and also stimulating the FNDC5/irisin pathway. Interestingly, lactate-induced induction of the PGC1α/FNDC5/BDNF pathway appears to be dependent on SIRT1, although more investigation is required to confirm this. Exercise-induced BDNF upregulation reduces amyloidogenic Aβ levels. Mechanisms behind this reduction may be by reducing amyloidogenic andpromoting nonamyloidogenic cleavage of APP. Physical exercise is a cost-effective intervention that has demonstrated favorable outcomes in improving cognitive impairment in neurodegenerative diseases such as Alzheimer's disease. Reviewed here are a few of the many mechanisms involved in the beneficial effects of exercise on the brain. A comprehensive understanding of these mechanisms is key to developing biomarkers and therapeutics to slow cognitive decline.

Funding: SJ is supported by a scholarship from the McMaster Institute for Research in Aging (MIRA). MF is funded by grants from the Canadian Institutes of Health Research (CIHR), the Canadian Consortium on Neurodegeneration in Aging (CCNA), and the Natural Sciences and Engineering Research Council of Canada (NSERC).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. "2023 Alzheimer's disease facts and figures," Alzheimer's & Dementia, vol. 19, no. 4, pp. 1598–1695, 2023, doi: 10.1002/alz.13016.
2. C. A. Lane, J. Hardy, and J. M. Schott, "Alzheimer's disease," European Journal of Neurology, vol. 25, no. 1, pp. 59–70, 2018, doi: 10.1111/ene.13439.
3. L. Crews and E. Masliah, "Molecular mechanisms of neurodegeneration in Alzheimer's disease," Hum Mol Genet, vol. 19, no. R1, pp. R12–R20, Apr. 2010, doi: 10.1093/hmg/ddq160.
4. S. S. Sisodia and D. L. Price, "Role of the beta-amyloid protein in Alzheimer's disease," FASEB J, vol. 9, no. 5, pp. 366–370, Mar. 1995, doi: 10.1096/fasebj.9.5.7896005.
5. D. J. Selkoe, "Amyloid beta protein precursor and the pathogenesis of Alzheimer's disease," Cell, vol. 58, no. 4, pp. 611–612, Aug. 1989, doi: 10.1016/0092-8674(89)90093-7.
6. C. Mori et al., "Intraneuronal Abeta42 accumulation in Down syndrome brain," Amyloid, vol. 9, no. 2, pp. 88–102, Jun. 2002.
7. G. K. Gouras et al., "Intraneuronal Abeta42 accumulation in human brain," Am J Pathol, vol. 156, no. 1, pp. 15–20, Jan. 2000, doi: 10.1016/s0002-9440(10)64700-1.
8. T. A. Bayer et al., "Key factors in Alzheimer's disease: beta-amyloid precursor protein processing, metabolism and intraneuronal transport," Brain Pathol, vol. 11, no. 1, pp. 1–11, Jan. 2001, doi: 10.1111/j.1750-3639.2001.tb00376.x.
9. Y. Zhang, R. McLaughlin, C. Goodyer, and A. LeBlanc, "Selective cytotoxicity of intracellular amyloid β peptide1–42 through p53 and Bax in cultured primary human neurons," Journal of Cell Biology, vol. 156, no. 3, pp. 519–529, Jan. 2002, doi: 10.1083/jcb.200110119.
10. D. H. Chui et al., "Apoptotic neurons in Alzheimer's disease frequently show intracellular Abeta42 labeling," J Alzheimers Dis, vol. 3, no. 2, pp. 231–239, Apr. 2001, doi: 10.3233/jad-2001-3208.
11. M. Fahnestock, "BDNF: The link between beta-amyloid and memory loss," 2011, doi: 10.2217/FNL.11.44.
12. B. Lu, G. Nagappan, and Y. Lu, "BDNF and Synaptic Plasticity, Cognitive Function, and Dysfunction," in Neurotrophic Factors, G. R. Lewin and B. D. Carter, Eds., in Handbook of Experimental Pharmacology. Berlin, Heidelberg: Springer, 2014, pp. 223–250. doi: 10.1007/978-3-642-45106-5_9.
13. D. K. BINDER and H. E. SCHARFMAN, "Brain-derived Neurotrophic Factor," Growth Factors, vol. 22, no. 3, pp. 123–131, Sep. 2004, doi: 10.1080/08977190410001723308.
14. E. J. Huang and L. F. Reichardt, "Neurotrophins: Roles in Neuronal Development and Function," Annu Rev Neurosci, vol. 24, pp. 677–736, 2001, doi: 10.1146/annurev.neuro.24.1.677.
15. V. Pencea, K. D. Bingaman, S. J. Wiegand, and M. B. Luskin, "Infusion of Brain-Derived Neurotrophic Factor into the Lateral Ventricle of the Adult Rat Leads to New Neurons in the Parenchyma of the Striatum,

Septum, Thalamus, and Hypothalamus," J Neurosci, vol. 21, no. 17, pp. 6706–6717, Sep. 2001, doi: 10.1523/JNEUROSCI.21-17-06706.2001.
16. Y. Lu, K. Christian, and B. Lu, "BDNF: A Key Regulator for Protein-synthesis Dependent LTP and Long-term Memory?," Neurobiol Learn Mem, vol. 89, no. 3, pp. 312–323, Mar. 2008, doi: 10.1016/j.nlm.2007.08.018.
17. S. Peng, J. Wuu, E. J. Mufson, and M. Fahnestock, "Precursor form of brain-derived neurotrophic factor and mature brain-derived neurotrophic factor are decreased in the pre-clinical stages of Alzheimer's disease," J Neurochem, vol. 93, no. 6, pp. 1412–1421, Jun. 2005, doi: 10.1111/j.1471-4159.2005.03135.x.
18. J. Siuda et al., "Cognitive impairment and BDNF serum levels," Neurol Neurochir Pol, vol. 51, no. 1, pp. 24–32, 2017, doi: 10.1016/j.pjnns.2016.10.001.
19. B. Michalski and M. Fahnestock, "Pro-brain-derived neurotrophic factor is decreased in parietal cortex in Alzheimer's disease," Brain Res Mol Brain Res, vol. 111, no. 1–2, pp. 148–154, Mar. 2003, doi: 10.1016/s0169-328x(03)00003-2.
20. P. Pruunsild, M. Sepp, E. Orav, I. Koppel, and T. Timmusk, "Identification of cis-elements and transcription factors regulating neuronal activity-dependent transcription of human BDNF gene," J Neurosci, vol. 31, no. 9, pp. 3295–3308, Mar. 2011, doi: 10.1523/JNEUROSCI.4540-10.2011.
21. E.-E. Esvald, J. Tuvikene, A. Sirp, S. Patil, C. R. Bramham, and T. Timmusk, "CREB Family Transcription Factors Are Major Mediators of BDNF Transcriptional Autoregulation in Cortical Neurons," J Neurosci, vol. 40, no. 7, pp. 1405–1426, Feb. 2020, doi: 10.1523/JNEUROSCI.0367-19.2019.
22. G. Moya-Alvarado et al., "BDNF/TrkB signaling endosomes in axons coordinate CREB/mTOR activation and protein synthesis in the cell body to induce dendritic growth in cortical neurons," eLife, vol. 12, p. e77455, Feb. 2023, doi: 10.7554/eLife.77455.
23. R. K. Narasimhamurthy, D. Andrade, and K. D. Mumbrekar, "Modulation of CREB and its associated upstream signaling pathways in pesticide-induced neurotoxicity," Mol Cell Biochem, vol. 477, no. 11, pp. 2581–2593, 2022, doi: 10.1007/s11010-022-04472-7.
24. O. V. Vitolo, A. Sant'Angelo, V. Costanzo, F. Battaglia, O. Arancio, and M. Shelanski, "Amyloid β-peptide inhibition of the PKA/CREB pathway and long-term potentiation: Reversibility by drugs that enhance cAMP signaling," Proceedings of the National Academy of Sciences of the United States of America, vol. 99, no. 20, pp. 13217–13221, 2002, doi: 10.1073/pnas.172504199.
25. D. J. Garzon and M. Fahnestock, "Oligomeric Amyloid Decreases Basal Levels of Brain-Derived Neurotrophic factor (BDNF) mRNA via Specific Downregulation of BDNF Transcripts IV and V in Differentiated Human Neuroblastoma Cells," J Neurosci, vol. 27, no. 10, pp. 2628–2635, Mar. 2007, doi: 10.1523/JNEUROSCI.5053-06.2007.
26. E. Rosa and M. Fahnestock, "CREB expression mediates amyloid β-induced basal BDNF downregulation," Neurobiology of Aging, vol. 36, no. 8, pp. 2406–2413, Aug. 2015, doi: 10.1016/j.neurobiolaging.2015.04.014.
27. J. C. Belrose, R. Masoudi, B. Michalski, and M. Fahnestock, "Increased pro-nerve growth factor and decreased brain-derived neurotrophic factor in non-Alzheimer's disease tauopathies," Neurobiol Aging, vol. 35, no. 4, pp. 926–933, Apr. 2014, doi: 10.1016/j.neurobiolaging.2013.08.029.
28. E. Rosa, S. Mahendram, Y. D. Ke, L. M. Ittner, S. D. Ginsberg, and M. Fahnestock, "Tau downregulates BDNF expression in animal and cellular models of Alzheimer's disease," Neurobiol Aging, vol. 48, pp. 135–142, Dec. 2016, doi: 10.1016/j.neurobiolaging.2016.08.020.
29. J. Ye et al., "Tau inhibits PKA by nuclear proteasome-dependent PKAR2α elevation with suppressed CREB/GluA1 phosphorylation," Aging Cell, vol. 19, no. 1, p. e13055, Jan. 2020, doi: 10.1111/acel.13055.
30. C. W. Cotman, N. C. Berchtold, and L.-A. Christie, "Exercise builds brain health: key roles of growth factor cascades and inflammation," Trends Neurosci, vol. 30, no. 9, pp. 464–472, Sep. 2007, doi: 10.1016/j.tins.2007.06.011.
31. M. W. Voss, L. S. Nagamatsu, T. Liu-Ambrose, and A. F. Kramer, "Exercise, brain, and cognition across the life span," Journal of Applied Physiology, vol. 111, no. 5, pp. 1505–1513, Nov. 2011, doi: 10.1152/japplphysiol.00210.2011.
32. K. I. Erickson, R. L. Leckie, and A. M. Weinstein, "Physical activity, fitness, and gray matter volume," Neurobiol Aging, vol. 35 Suppl 2, pp. S20-28, Sep. 2014, doi: 10.1016/j.neurobiolaging.2014.03.034.
33. C. W. Cotman and N. C. Berchtold, "Exercise: a behavioral intervention to enhance brain health and plasticity," Trends in Neurosciences, vol. 25, no. 6, pp. 295–301, Jun. 2002, doi: 10.1016/S0166-2236(02)02143-4.
34. P. Bekinschtein, C. A. Oomen, L. M. Saksida, and T. J. Bussey, "Effects of environmental enrichment and voluntary exercise on neurogenesis, learning and memory, and pattern separation: BDNF as a critical variable?," Seminars in Cell & Developmental Biology, vol. 22, no. 5, pp. 536–542, Jul. 2011, doi: 10.1016/j.semcdb.2011.07.002.
35. F. M et al., "BDNF increases with behavioral enrichment and an antioxidant diet in the aged dog," Neurobiology of aging, vol. 33, no. 3, Mar. 2012, doi: 10.1016/j.neurobiolaging.2010.03.019.

36. J. K. Morris et al., “Aerobic exercise for Alzheimer’s disease: A randomized controlled pilot trial,” PLoS One, vol. 12, no. 2, p. e0170547, 2017, doi: 10.1371/journal.pone.0170547.
37. J. Tao et al., “Mind-body exercise improves cognitive function and modulates the function and structure of the hippocampus and anterior cingulate cortex in patients with mild cognitive impairment,” Neuroimage Clin, vol. 23, p. 101834, 2019, doi: 10.1016/j.nicl.2019.101834.
38. M. E. Johansson et al., “Aerobic Exercise Alters Brain Function and Structure in Parkinson’s Disease: A Randomized Controlled Trial,” Ann Neurol, vol. 91, no. 2, pp. 203–216, Feb. 2022, doi: 10.1002/ana.26291.
39. T. Tarumi et al., “Aerobic exercise training and neurocognitive function in cognitively normal older adults: A one-year randomized controlled trial,” J Intern Med, vol. 292, no. 5, pp. 788–803, Nov. 2022, doi: 10.1111/joim.13534.
40. L. M. J. Sanders, T. Hortobágyi, E. G. A. Karssemeijer, E. A. Van der Zee, E. J. A. Scherder, and M. J. G. van Heuvelen, “Effects of low- and high-intensity physical exercise on physical and cognitive function in older persons with dementia: a randomized controlled trial,” Alzheimers Res Ther, vol. 12, no. 1, p. 28, Mar. 2020, doi: 10.1186/s13195-020-00597-3.
41. E. J. Lenze et al., “Effects of Mindfulness Training and Exercise on Cognitive Function in Older Adults: A Randomized Clinical Trial,” JAMA, vol. 328, no. 22, pp. 2218–2229, Dec. 2022, doi: 10.1001/jama.2022.21680.
42. S. E. Lamb et al., “Dementia And Physical Activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: randomised controlled trial,” BMJ, vol. 361, p. k1675, May 2018, doi: 10.1136/bmj.k1675.
43. N. Gates, M. A. Fiatarone Singh, P. S. Sachdev, and M. Valenzuela, “The effect of exercise training on cognitive function in older adults with mild cognitive impairment: a meta-analysis of randomized controlled trials,” Am J Geriatr Psychiatry, vol. 21, no. 11, pp. 1086–1097, Nov. 2013, doi: 10.1016/j.jagp.2013.02.018.
44. G. A. Panza et al., “Can Exercise Improve Cognitive Symptoms of Alzheimer’s Disease?,” J Am Geriatr Soc, vol. 66, no. 3, pp. 487–495, Mar. 2018, doi: 10.1111/jgs.15241.
45. H. Öhman et al., “Effects of Exercise on Cognition: The Finnish Alzheimer Disease Exercise Trial: A Randomized, Controlled Trial,” Journal of the American Geriatrics Society, vol. 64, no. 4, pp. 731–738, 2016, doi: 10.1111/jgs.14059.
46. L. C. Venegas-Sanabria, I. Cavero-Redondo, V. Martínez-Vizcaino, C. A. Cano-Gutierrez, and C. Álvarez-Bueno, “Effect of multicomponent exercise in cognitive impairment: a systematic review and meta-analysis,” BMC Geriatr, vol. 22, no. 1, p. 617, Jul. 2022, doi: 10.1186/s12877-022-03302-1.
47. K. L. Szuhany, M. Bugatti, and M. W. Otto, “A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor,” J Psychiatr Res, vol. 60, pp. 56–64, Jan. 2015, doi: 10.1016/j.jpsychires.2014.10.003.
48. C. Ma et al., “The impact of physical activity on blood inflammatory cytokines and neuroprotective factors in individuals with mild cognitive impairment: a systematic review and meta-analysis of randomized-controlled trials,” Aging Clin Exp Res, vol. 34, no. 7, pp. 1471–1484, Jul. 2022, doi: 10.1007/s40520-021-02069-6.
49. C. G. Causing et al., “Synaptic innervation density is regulated by neuron-derived BDNF,” Neuron, vol. 18, no. 2, pp. 257–267, Feb. 1997, doi: 10.1016/s0896-6273(00)80266-4.
50. H. W. Horch, A. Krüttgen, S. D. Portbury, and L. C. Katz, “Destabilization of cortical dendrites and spines by BDNF,” Neuron, vol. 23, no. 2, pp. 353–364, Jun. 1999, doi: 10.1016/s0896-6273(00)80785-0.
51. B. Lu, “BDNF and activity-dependent synaptic modulation,” Learn Mem, vol. 10, no. 2, pp. 86–98, 2003, doi: 10.1101/lm.54603.
52. H. E. Scharfman, “Hyperexcitability in Combined Entorhinal/Hippocampal Slices of Adult Rat After Exposure to Brain-Derived Neurotrophic Factor,” Journal of Neurophysiology, vol. 78, no. 2, pp. 1082–1095, Aug. 1997, doi: 10.1152/jn.1997.78.2.1082.
53. C. Verpelli et al., “Synaptic Activity Controls Dendritic Spine Morphology by Modulating eEF2-Dependent BDNF Synthesis,” J Neurosci, vol. 30, no. 17, pp. 5830–5842, Apr. 2010, doi: 10.1523/JNEUROSCI.0119-10.2010.
54. S. A. Neeper, F. Gómez-Pinilla, J. Choi, and C. W. Cotman, “Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain,” Brain Research, vol. 726, no. 1, pp. 49–56, Jul. 1996, doi: 10.1016/0006-8993(96)00273-9.
55. S. A. Neeper, F. Góauctemez-Pinilla, J. Choi, and C. Cotman, “Exercise and brain neurotrophins,” Nature, vol. 373, no. 6510, Art. no. 6510, Jan. 1995, doi: 10.1038/373109a0.
56. F. Gómez-Pinilla, Z. Ying, P. Opazo, R. R. Roy, and V. R. Edgerton, “Differential regulation by exercise of BDNF and NT-3 in rat spinal cord and skeletal muscle,” European Journal of Neuroscience, vol. 13, no. 6, pp. 1078–1084, 2001, doi: 10.1046/j.0953-816x.2001.01484.x.
57. F. G. de M. Coelho, S. Gobbi, C. A. A. Andreatto, D. I. Corazza, R. V. Pedroso, and R. F. Santos-Galduróz, “Physical exercise modulates peripheral levels of brain-derived neurotrophic factor (BDNF): a systematic

review of experimental studies in the elderly," Arch Gerontol Geriatr, vol. 56, no. 1, pp. 10–15, 2013, doi: 10.1016/j.archger.2012.06.003.
58. C. Laske et al., "Exercise-induced normalization of decreased BDNF serum concentration in elderly women with remitted major depression," Int J Neuropsychopharmacol, vol. 13, no. 5, pp. 595–602, Jun. 2010, doi: 10.1017/S1461145709991234.
59. C. Nicolini et al., "A Single Bout of High-intensity Interval Exercise Increases Corticospinal Excitability, Brain-derived Neurotrophic Factor, and Uncarboxylated Osteolcalcin in Sedentary, Healthy Males," Neuroscience, vol. 437, pp. 242–255, Jun. 2020, doi: 10.1016/j.neuroscience.2020.03.042.
60. C.-L. Tsai, F.-C. Chen, C.-Y. Pan, C.-H. Wang, T.-H. Huang, and T.-C. Chen, "Impact of acute aerobic exercise and cardiorespiratory fitness on visuospatial attention performance and serum BDNF levels," Psychoneuroendocrinology, vol. 41, pp. 121–131, Mar. 2014, doi: 10.1016/j.psyneuen.2013.12.014.
61. K. Håkansson et al., "BDNF Responses in Healthy Older Persons to 35 Minutes of Physical Exercise, Cognitive Training, and Mindfulness: Associations with Working Memory Function," J Alzheimers Dis, vol. 55, no. 2, pp. 645–657, 2017, doi: 10.3233/JAD-160593.
62. H. Fujimura et al., "Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation," Thromb Haemost, vol. 87, no. 4, pp. 728–734, Apr. 2002.
63. J. J. Walsh and M. E. Tschakovsky, "Exercise and circulating BDNF: Mechanisms of release and implications for the design of exercise interventions," Applied Physiology, Nutrition, and Metabolism, vol. 43, no. 11, pp. 1095–1105, Nov. 2018, doi: 10.1139/apnm-2018-0192.
64. W. Pan, W. A. Banks, M. B. Fasold, J. Bluth, and A. J. Kastin, "Transport of brain-derived neurotrophic factor across the blood–brain barrier," Neuropharmacology, vol. 37, no. 12, pp. 1553–1561, Dec. 1998, doi: 10.1016/S0028-3908(98)00141-5.
65. P. Rasmussen et al., "Evidence for a release of brain-derived neurotrophic factor from the brain during exercise," Exp Physiol, vol. 94, no. 10, pp. 1062–1069, Oct. 2009, doi: 10.1113/expphysiol.2009.048512.
66. W. M. Pardridge, Y. S. Kang, and J. L. Buciak, "Transport of human recombinant brain-derived neurotrophic factor (BDNF) through the rat blood-brain barrier in vivo using vector-mediated peptide drug delivery," Pharm Res, vol. 11, no. 5, pp. 738–746, May 1994, doi: 10.1023/a:1018940732550.
67. A. B. Klein et al., "Blood BDNF concentrations reflect brain-tissue BDNF levels across species," International Journal of Neuropsychopharmacology, vol. 14, no. 3, pp. 347–353, Apr. 2011, doi: 10.1017/S1461145710000738.
68. A. Sartorius et al., "Correlations and Discrepancies between Serum and Brain Tissue Levels of Neurotrophins after Electroconvulsive Treatment in Rats," Pharmacopsychiatry, vol. 42, no. 6, pp. 270–276, 2009, doi: 10.1055/s-0029-1224162.
69. F. Karege, M. Schwald, and M. Cisse, "Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets," Neuroscience Letters, vol. 328, no. 3, pp. 261–264, Aug. 2002, doi: 10.1016/S0304-3940(02)00529-3.
70. A. Want, J. E. Morgan, and Y.-A. Barde, "Brain-derived neurotrophic factor measurements in mouse serum and plasma using a sensitive and specific enzyme-linked immunosorbent assay," Sci Rep, vol. 13, no. 1, p. 7740, May 2023, doi: 10.1038/s41598-023-34262-0.
71. J. J. Heisz et al., "The Effects of Physical Exercise and Cognitive Training on Memory and Neurotrophic Factors," J Cogn Neurosci, vol. 29, no. 11, pp. 1895–1907, Nov. 2017, doi: 10.1162/jocn_a_01164.
72. H. Arazi, P. Babaei, M. Moghimi, and A. Asadi, "Acute effects of strength and endurance exercise on serum BDNF and IGF-1 levels in older men," BMC Geriatr, vol. 21, no. 1, p. 50, Jan. 2021, doi: 10.1186/s12877-020-01937-6.
73. M. J. Wheeler et al., "Distinct effects of acute exercise and breaks in sitting on working memory and executive function in older adults: a three-arm, randomised cross-over trial to evaluate the effects of exercise with and without breaks in sitting on cognition," Br J Sports Med, vol. 54, no. 13, pp. 776–781, Jul. 2020, doi: 10.1136/bjsports-2018-100168.
74. F. M. Coelho et al., "Physical therapy intervention (PTI) increases plasma brain-derived neurotrophic factor (BDNF) levels in non-frail and pre-frail elderly women," Arch Gerontol Geriatr, vol. 54, no. 3, pp. 415–420, 2012, doi: 10.1016/j.archger.2011.05.014.
75. R. Ruscheweyh et al., "Physical activity and memory functions: an interventional study," Neurobiol Aging, vol. 32, no. 7, pp. 1304–1319, Jul. 2011, doi: 10.1016/j.neurobiolaging.2009.08.001.
76. A. Kovacevic, B. Fenesi, E. Paolucci, and J. J. Heisz, "The effects of aerobic exercise intensity on memory in older adults," Appl Physiol Nutr Metab, vol. 45, no. 6, pp. 591–600, Jun. 2020, doi: 10.1139/apnm-2019-0495.
77. K. I. Erickson et al., "Exercise training increases size of hippocampus and improves memory," Proc Natl Acad Sci U S A, vol. 108, no. 7, pp. 3017–3022, Feb. 2011, doi: 10.1073/pnas.1015950108.
78. S. C. Moser and B. C. J. van der Eerden, "Osteocalcin—A Versatile Bone-Derived Hormone," Frontiers in Endocrinology, vol. 9, 2019, Accessed: Jul. 22, 2023. [Online]. Available: https://www.frontiersin.org/articles/10.3389/fendo.2018.00794

79. S. Aktitiz, M. M. Atakan, H. H. Turnagöl, and Ş. N. Koşar, "Interleukin-6, undercarboxylated osteocalcin, and brain-derived neurotrophic factor responses to single and repeated sessions of high-intensity interval exercise," Peptides, vol. 157, p. 170864, Nov. 2022, doi: 10.1016/j.peptides.2022.170864.
80. I. Levinger et al., "The Effect of Acute Exercise on Undercarboxylated Osteocalcin and Insulin Sensitivity in Obese Men," Journal of Bone and Mineral Research, vol. 29, no. 12, pp. 2571–2576, 2014, doi: 10.1002/jbmr.2285.
81. S. Chowdhury et al., "Muscle-derived interleukin 6 increases exercise capacity by signaling in osteoblasts," J Clin Invest, vol. 130, no. 6, pp. 2888–2902, Jun. 2020, doi: 10.1172/JCI133572.
82. F. Oury et al., "Maternal and offspring pools of osteocalcin influence brain development and functions," Cell, vol. 155, no. 1, pp. 228–241, Sep. 2013, doi: 10.1016/j.cell.2013.08.042.
83. M. Nakamura, M. Imaoka, and M. Takeda, "Interaction of bone and brain: osteocalcin and cognition," International Journal of Neuroscience, vol. 131, no. 11, pp. 1115–1123, 2021, doi: 10.1080/00207454.2020.1770247.
84. S. A. Villeda et al., "Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice," Nat Med, vol. 20, no. 6, pp. 659–663, Jun. 2014, doi: 10.1038/nm.3569.
85. L. Khrimian et al., "Gpr158 mediates osteocalcin's regulation of cognition," J Exp Med, vol. 214, no. 10, pp. 2859–2873, Oct. 2017, doi: 10.1084/jem.20171320.
86. K. Mikoshiba, "IP3 receptor/Ca2+ channel: from discovery to new signaling concepts," Journal of Neurochemistry, vol. 102, no. 5, pp. 1426–1446, 2007, doi: 10.1111/j.1471-4159.2007.04825.x.
87. K. Sato et al., "Regulation of osteoclast differentiation and function by the CaMK-CREB pathway," Nat Med, vol. 12, no. 12, Art. no. 12, Dec. 2006, doi: 10.1038/nm1515.
88. S. Kosmidis et al., "RbAp48 Protein Is a Critical Component of GPR158/OCN Signaling and Ameliorates Age-Related Memory Loss," Cell Rep, vol. 25, no. 4, pp. 959-973.e6, Oct. 2018, doi: 10.1016/j.celrep.2018.09.077.
89. Q. Zhang, N. Vo, and R. H. Goodman, "Histone Binding Protein RbAp48 Interacts with a Complex of CREB Binding Protein and Phosphorylated CREB," Mol Cell Biol, vol. 20, no. 14, pp. 4970–4978, Jul. 2000.
90. E. Korzus, M. G. Rosenfeld, and M. Mayford, "CBP Histone Acetyltransferase Activity Is a Critical Component of Memory Consolidation," Neuron, vol. 42, no. 6, pp. 961–972, Jun. 2004, doi: 10.1016/j.neuron.2004.06.002.
91. S. Peleg et al., "Altered Histone Acetylation Is Associated with Age-Dependent Memory Impairment in Mice," Science, vol. 328, no. 5979, pp. 753–756, May 2010, doi: 10.1126/science.1186088.
92. C. G. Vecsey et al., "Histone deacetylase inhibitors enhance memory and synaptic plasticity via CREB:CBP-dependent transcriptional activation," J Neurosci, vol. 27, no. 23, pp. 6128–6140, Jun. 2007, doi: 10.1523/JNEUROSCI.0296-07.2007.
93. K. Panati, Y. Suneetha, and V. R. Narala, "Irisin/FNDC5--An updated review," Eur Rev Med Pharmacol Sci, vol. 20, no. 4, pp. 689–697, 2016.
94. M. V. Lourenco et al., "Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models," Nat Med, vol. 25, no. 1, pp. 165–175, Jan. 2019, doi: 10.1038/s41591-018-0275-4.
95. C. D. Wrann et al., "Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway," Cell Metab, vol. 18, no. 5, pp. 649–659, Nov. 2013, doi: 10.1016/j.cmet.2013.09.008.
96. M.-S. Hashemi et al., "Fndc5 knockdown significantly decreased neural differentiation rate of mouse embryonic stem cells," Neuroscience, vol. 231, pp. 296–304, Feb. 2013, doi: 10.1016/j.neuroscience.2012.11.041.
97. M. R. Islam et al., "Exercise hormone irisin is a critical regulator of cognitive function," Nat Metab, vol. 3, no. 8, pp. 1058–1070, Aug. 2021, doi: 10.1038/s42255-021-00438-z.
98. P. Boström et al., "A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis," Nature, vol. 481, no. 7382, pp. 463–468, Jan. 2012, doi: 10.1038/nature10777.
99. J. Park, J. Kim, and T. Mikami, "Exercise hormone irisin prevents physical inactivity-induced cognitive decline in mice," Behav Brain Res, vol. 433, p. 114008, Sep. 2022, doi: 10.1016/j.bbr.2022.114008.
100. N. Vijay and M. E. Morris, "Role of Monocarboxylate Transporters in Drug Delivery to the Brain," Curr Pharm Des, vol. 20, no. 10, pp. 1487–1498, 2014.
101. L. Riske, R. K. Thomas, G. B. Baker, and S. M. Dursun, "Lactate in the brain: an update on its relevance to brain energy, neurons, glia and panic disorder," Ther Adv Psychopharmacol, vol. 7, no. 2, pp. 85–89, Feb. 2017, doi: 10.1177/2045125316675579.
102. A. Suzuki et al., "Astrocyte-neuron lactate transport is required for long-term memory formation," Cell, vol. 144, no. 5, pp. 810–823, Mar. 2011, doi: 10.1016/j.cell.2011.02.018.
103. P. J. Magistretti and I. Allaman, "Lactate in the brain: from metabolic end-product to signalling molecule," Nat Rev Neurosci, vol. 19, no. 4, Art. no. 4, Apr. 2018, doi: 10.1038/nrn.2018.19.
104. L. Pellerin and P. J. Magistretti, "Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization," Proc Natl Acad Sci U S A, vol. 91, no. 22, pp. 10625–10629, Oct. 1994, doi: 10.1073/pnas.91.22.10625.

105. M. Q. Steinman, V. Gao, and C. M. Alberini, "The Role of Lactate-Mediated Metabolic Coupling between Astrocytes and Neurons in Long-Term Memory Formation," Frontiers in Integrative Neuroscience, vol. 10, 2016, Accessed: Aug. 05, 2023. [Online]. Available: https://www.frontiersin.org/articles/10.3389/fnint.2016.00010
106. L. A. Newman, D. L. Korol, and P. E. Gold, "Lactate Produced by Glycogenolysis in Astrocytes Regulates Memory Processing," PLOS ONE, vol. 6, no. 12, p. e28427, Dec. 2011, doi: 10.1371/journal.pone.0028427.
107. P. Müller, Y. Duderstadt, V. Lessmann, and N. G. Müller, "Lactate and BDNF: Key Mediators of Exercise Induced Neuroplasticity?," J Clin Med, vol. 9, no. 4, p. 1136, Apr. 2020, doi: 10.3390/jcm9041136.
108. J. Yang et al., "Lactate promotes plasticity gene expression by potentiating NMDA signaling in neurons," Proc Natl Acad Sci U S A, vol. 111, no. 33, pp. 12228–12233, Aug. 2014, doi: 10.1073/pnas.1322912111.
109. L. El Hayek 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, vol. 39, no. 13, pp. 2369–2382, Mar. 2019, doi: 10.1523/JNEUROSCI.1661-18.2019.
110. Q. Chen et al., "Differential Roles of NR2A- and NR2B-Containing NMDA Receptors in Activity-Dependent Brain-Derived Neurotrophic Factor Gene Regulation and Limbic Epileptogenesis," J. Neurosci., vol. 27, no. 3, pp. 542–552, Jan. 2007, doi: 10.1523/JNEUROSCI.3607-06.2007.
111. W. Yao et al., "Microglial ERK-NRBP1-CREB-BDNF signaling in sustained antidepressant actions of (R)-ketamine," Mol Psychiatry, vol. 27, no. 3, pp. 1618–1629, Mar. 2022, doi: 10.1038/s41380-021-01377-7.
112. G. Krapivinsky et al., "The NMDA Receptor Is Coupled to the ERK Pathway by a Direct Interaction between NR2B and RasGRF1," Neuron, vol. 40, no. 4, pp. 775–784, Nov. 2003, doi: 10.1016/S0896-6273(03)00645-7.
113. D. Laurin, R. Verreault, J. Lindsay, K. MacPherson, and K. Rockwood, "Physical Activity and Risk of Cognitive Impairment and Dementia in Elderly Persons," Archives of Neurology, vol. 58, no. 3, pp. 498–504, Mar. 2001, doi: 10.1001/archneur.58.3.498.
114. R. P. Friedland et al., "Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members," Proceedings of the National Academy of Sciences, vol. 98, no. 6, pp. 3440–3445, Mar. 2001, doi: 10.1073/pnas.061002998.
115. Y. Rolland, G. A. van Kan, and B. Vellas, "Physical Activity and Alzheimer's Disease: From Prevention to Therapeutic Perspectives," Journal of the American Medical Directors Association, vol. 9, no. 6, pp. 390–405, Jul. 2008, doi: 10.1016/j.jamda.2008.02.007.
116. J. Alty, M. Farrow, and K. Lawler, "Exercise and dementia prevention," Pract Neurol, vol. 20, no. 3, pp. 234–240, May 2020, doi: 10.1136/practneurol-2019-002335.
117. M. Kivipelto, F. Mangialasche, and T. Ngandu, "Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease," Nat Rev Neurol, vol. 14, no. 11, pp. 653–666, Nov. 2018, doi: 10.1038/s41582-018-0070-3.
118. B. M. Brown et al., "Physical activity and amyloid-β plasma and brain levels: results from the Australian Imaging, Biomarkers and Lifestyle Study of Ageing," Mol Psychiatry, vol. 18, no. 8, Art. no. 8, Aug. 2013, doi: 10.1038/mp.2012.107.
119. S. Arancibia et al., "Protective effect of BDNF against beta-amyloid induced neurotoxicity in vitro and in vivo in rats," Neurobiology of Disease, vol. 31, no. 3, pp. 316–326, Sep. 2008, doi: 10.1016/j.nbd.2008.05.012.
120. C. Matrone, M. T. Ciotti, D. Mercanti, R. Marolda, and P. Calissano, "NGF and BDNF signaling control amyloidogenic route and Aβ production in hippocampal neurons," Proc Natl Acad Sci U S A, vol. 105, no. 35, pp. 13139–13144, Sep. 2008, doi: 10.1073/pnas.0806133105.
121. Z.-H. Wang et al., "Deficiency in BDNF/TrkB Neurotrophic Activity Stimulates δ-Secretase by Upregulating C/EBPβ in Alzheimer's Disease," Cell Rep, vol. 28, no. 3, pp. 655-669.e5, Jul. 2019, doi: 10.1016/j.celrep.2019.06.054.
122. V. W. Chow, M. P. Mattson, P. C. Wong, and M. Gleichmann, "An Overview of APP Processing Enzymes and Products," Neuromolecular Med, vol. 12, no. 1, pp. 1–12, Mar. 2010, doi: 10.1007/s12017-009-8104-z.
123. Z. Zhang et al., "Delta-secretase cleaves amyloid precursor protein and regulates the pathogenesis in Alzheimer's disease," Nat Commun, vol. 6, p. 8762, Nov. 2015, doi: 10.1038/ncomms9762.
124. Z.-H. Wang et al., "BDNF inhibits neurodegenerative disease-associated asparaginyl endopeptidase activity via phosphorylation by AKT," JCI insight, vol. 3, no. 16, 2018, doi: 10.1172/jci.insight.99007.
125. B. J. Baranowski, G. C. Hayward, D. M. Marko, and R. E. K. MacPherson, "Examination of BDNF Treatment on BACE1 Activity and Acute Exercise on Brain BDNF Signaling," Frontiers in Cellular Neuroscience, vol. 15, 2021, Accessed: Jul. 19, 2023. [Online]. Available: https://www.frontiersin.org/articles/10.3389/fncel.2021.665867
126. B. J. Baranowski et al., "Exercise training and BDNF injections alter amyloid precursor protein (APP) processing enzymes and improve cognition," J Appl Physiol (1985), vol. 135, no. 1, pp. 121–135, Jul. 2023, doi: 10.1152/japplphysiol.00114.2023.

127. S. Lammich et al., "Constitutive and regulated alpha-secretase cleavage of Alzheimer's amyloid precursor protein by a disintegrin metalloprotease," Proc Natl Acad Sci U S A, vol. 96, no. 7, pp. 3922–3927, Mar. 1999, doi: 10.1073/pnas.96.7.3922.
128. S. M. Nigam, S. Xu, J. S. Kritikou, K. Marosi, L. Brodin, and M. P. Mattson, "Exercise and BDNF reduce Aβ production by enhancing α-secretase processing of APP," J Neurochem, vol. 142, no. 2, pp. 286–296, Jul. 2017, doi: 10.1111/jnc.14034.