Review Article

Promoting brain health in older adults through exercise: A narrative review of the role of muscle-brain crosstalk

Safoura Alizade[1], Mohammad Faramarzi[1*]

Abstract

This article explores the impact of exercise training on brain health in older adults, focusing on the concept of muscle-brain crosstalk. As the global population ages, understanding how lifestyle interventions like exercise can support cognitive function is increasingly important. The article reviews evidence suggesting that physical activity, particularly aerobic and resistance training, plays a crucial role in maintaining and enhancing brain health. It discusses the mechanisms underlying the beneficial effects of exercise, including improved blood flow, neurogenesis, and the release of myokines proteins produced by muscle contractions that influence brain function. Additionally, the article highlights how these myokines facilitate communication between muscles and the brain, contributing to neuroplasticity, reduced inflammation, and enhanced cognitive abilities. The concept of muscle-brain crosstalk is emphasized as a key factor in understanding how exercise promotes brain health, with potential implications for designing targeted interventions to preserve cognitive function in older adults. The article concludes by suggesting that regular exercise should be a cornerstone of public health strategies aimed at improving the quality of life and cognitive health in aging populations. Further research is encouraged to deepen our understanding of the molecular pathways involved and to develop personalized exercise programs that maximize brain health benefits for older adults.

Key Words: **Exercise training, Brain, Cognitive function, Myokines, Neuroplasticity, Muscle-brain crosstalk**

1. Department of Exercise Physiology, Faculty of Sport Sciences, University of Isfahan, Isfahan, Iran.

*Author for correspondence: m.faramarzi@spr.ui.ac.ir

S A: 0000-0003-0275-8248; M F: 0000-0002-5685-2275

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Introduction

It is well-established that global populations are aging rapidly, with the number of individuals over 65 reaching 962 million in 2018, accounting for 12.8% of the global population. Projections suggest that by 2050, this demographic will rise to 2.1 billion, comprising 16% of the world's population (Liu et al., 2020). Age is a major risk factor for neurological conditions like stroke and dementia, but even in 'healthy aging,' the brain undergoes structural and functional changes. Blood flow to grey and white matter decreases by 0.5% annually from early adulthood, and despite a slight increase in oxygen extraction, the cerebral metabolic rate of oxygen (CMRO2) declines as well (Braz & Fisher, 2016). Aging is associated with brain atrophy, altered neural signaling, and cognitive issues such as slower processing speed and reduced working memory (Jagust, 2013). While cognitive decline is a natural part of aging, the rate of decline varies among individuals, influenced by genetic, physiological, environmental, and lifestyle factors, all of which are connected to brain structural (Jackson et al., 2016).

The purpose of this review is to explore how exercise can promote brain health in aging populations through mechanisms such as muscle-brain crosstalk. Recent research points to the beneficial effects of exercise on cognitive and brain health. Increasing physical activity, particularly regular aerobic exercise, can lower the risk of several age-related diseases. Exercise positively impacts various body systems, leading to changes in blood and hormone levels, while also improving cognitive abilities (Sanchez-Lopez et al., 2018). Evidence from epidemiological studies underscores the long-term benefits of consistent physical activity, linking it with reduced risks of type II diabetes (Dipla et al., 2020), cardiovascular diseases, mortality (Tofas et al., 2020), and mental health issues (Tyndall et al., 2018). Additionally, higher levels of physical activity, serving as a neuroprotective factor, may help slow cognitive decline and reduce the risk of dementia in aging. Physical exercise not only affects bodily systems but also enhances cognitive abilities like learning, memory, processing speed, and overall mental performance.

This review will focus on various dimensions of exercise, including type, intensity, and frequency, and their roles in supporting brain health outcomes, such as cognitive function and neuroplasticity. It concludes by identifying key areas for further research on this vital topic.

Physical activity and brain health

Exercise might prevent cognitive function decline and decrease age-related brain atrophy (Voss et al., 2013). Animal studies reveal that regular exercise, such as wheel-running in rats, results in less cognitive impairment on memory tests and enhances hippocampal neurogenesis and cortical angiogenesis, increasing oxygen supply to the brain (Creer et al., 2010). In humans, physical activity particularly aerobic and resistance training has been shown to benefit brain structure and function, especially within the hippocampus, a region integral to learning and memory and whose accelerated atrophy is associated with Alzheimer's disease (AD). Studies have demonstrated that increased physical activity is associated with larger hippocampal and frontal cortex volumes (Erickson et al., 2009).

A study involving a year-long, moderate-intensity walking intervention with inactive older adults resulted in a 2% increase in hippocampal volume, improvements in VO2 max, and elevated levels of Brain-Derived Neurotrophic Factor (BDNF) (Erickson et al., 2011). This finding aligns with subsequent studies that associate fitness improvements with hippocampal volume, spatial memory enhancements, and heightened BDNF levels (Ten Brinke et al., 2015). Physical activity results in increased brain volume and enhanced network connectivity. A study on older adults after one year of walking exercise reported no improvement in gray matter integrity, but the maximum oxygen consumption (VO_{2max}) in the walking group was linked with white matter integrity in the frontal lobes (Sexton et al., 2016).

As age, brain become increasingly vulnerable to reactive oxygen species (ROS) and inflammation, both of which heighten the risk of neurovascular diseases (Dutta et al., 2012). Conversely, regular exercise reduces oxidative stress and inflammation, supporting neurovascular health through enhanced antioxidant systems (García-Mesa et al., 2016).

A meta-analysis with sports intervention found that exercise is an effective strategy for enhancing cognitive function in older adults (Kramer & Colcombe, 2018). The impact of physical activity on brain health and cognition depends on the type, frequency, duration, and intensity of the exercise. Recent reports suggest that an increase in cerebrovascular reserve boosts the production of BDNF and NO, strengthens the nervous system and synaptogenesis, and maintains or even improves cognitive function (Davenport et al., 2012). Overall, physical activity fosters brain health and neuroplasticity by reducing vascular risks, impro-ving cerebral blood flow, and boosting neurotrophic support from factors like BDNF and IGF-1 (McGurran et al., 2019).

Additionally, exercise interventions offer benefits for those with dementia, including decreased risk of disability, falls, and neuropsychiatric symptoms (Dominguez et al., 2021). Studies report that exercise may reduce fall risk by approximately 31%, subsequently supporting daily functional independence in dementia patients (Demurtas et al., 2020).

Cognitive activity and brain health

Data from research frequently indicate that cognitive activity (CA) may offer benefits comparable to those of physical exercise. Specifically, studies have suggested a reduction in dementia among individuals involved in recreational, social, and professional activities (Mitchell et al., 2012). longitudinal studies revealed a significant correlation between participation in complex mental activities and the volume and size of the hippocampus over three years (Gidicsin et al., 2015; Wirth et al., 2014). Essentially, individuals who are physically active often engage in mental activities as well, making it challenging to distinguish the effects of physical activity from those of cognitive engagement (Robitaille et al., 2014). Preliminary studies suggest that targeted training activities aimed at enhancing executive functions may improve the efficiency of frontal networks. The observed improvement in neurological efficiency at low cognitive loads suggests a potential limitation in cognitive storage capacity, which may be suitable only for daily functional tasks (Heinzel et al., 2014). However, further research is needed to explore the impact of cognitive engagement on the daily functioning of older adults.

Synergistic benefits of combining cognitive and physical activity interventions

Combining physical and cognitive interventions appears to amplify cognitive benefits. A 16-week study with participants aged 60–85 found that those engaging in both exercise and cognitive training exhibited significantly better long-term memory compared to a control group (Shah et al., 2014). Similarly, Park et al. (2019) found that a combined program improved fitness, executive functioning, and working memory in older adults with Mild Cognitive Impairment (MCI) (Park et al., 2019). As noted, active older adults participating in combined activities show up to a 37% lower risk of dementia compared to less active peers (Karp et al., 2006). Combining physical and cognitive activities, therefore, represents a promising intervention model for cognitive and functional resilience in aging populations. (see Figure 1).

Suggested connections and possible underlying mechanisms between physical and cognitive activities that lead to improved physical and cognitive performance. The processes supporting

the link between cognitive engagement and cognitive function might be akin to those of physical activity and could involve enhanced cerebral blood circulation and neurogenesis.

Cerebral blood flow

Exercise improves cerebral blood flow (CBF) and oxygenation, both essential for maintaining cognitive functions (Liu & Brown, 2007). Research has shown that regular physical activity can improve cerebral perfusion and activate brain regions such as the sensory and motor areas, the cerebellum, and the motor cortex (Joris et al., 2018). Studies measuring CBF across different exercise intensities reveal that while blood flow increases during low to moderate exercise, it generally stabilizes during dynamic exercise (Joris et al., 2018).

In older adults, moderate to high-intensity exercise is linked with increased cerebral vasoconstriction. This response may either be a typical adaptation to exercise-induced high blood pressure, which is more common in the elderly, or a reflection of changes in vascular regulation. Despite these alterations, evidence suggests that brain perfusion remains optimized across different ages, both at rest and during exercise (Murrell et al., 2013). In summary, cerebral blood flow during exercise is modulated by the body's need to balance brain and muscle oxygenation. Moderate exercise enhances CBF to specific areas of the brain, but during high-intensity exercise, the brain's blood supply may become more constrained to maintain overall bodily function.

Impact of aerobic training on brain structure, function, and cognitive performance

Aerobic exercise positively impacts brain structure, function, and cognitive abilities by promoting learning and skill acquisition, improving white matter plasticity, and enhancing cerebral blood flow, which supports cognitive performance. Research indicates that aerobic exercise modifies neurotransmission, increasing the brain's responsiveness to new learning (Taubert et al., 2015). The findings indicate that aerobic exercise enhances neurotransmission by modifying the speed or timing of information transfer across large-scale networks involved in learning. Consequently, aerobic exercise may enhance the brain's adaptability to new stimuli, such as learning complex tasks (Lehmann et al., 2019). Increased blood flow, particularly to areas such as the hippocampus and frontal lobe, improves cognitive function (Maass et al., 2015; Stimpson et al., 2018). Therefore, the improved energy supply resulting from increased cerebral blood flow may facilitate changes in the brain's plasticity, supporting future learning (Lövdén et al., 2010). Exercise-induced brain-derived neurotrophic factor (BDNF) and lactate also support white matter and gray matter restructuring (El Hayek et al., 2019; Lehmann et al., 2020).

On a cellular level, aerobic exercise promotes mitochondrial biogenesis via PGC-1α, aiding energy production and reducing oxidative stress, particularly in the hippocampus. This is critical for cognitive health, including in neurodegenerative conditions like Alzheimer's (El Hayek et al., 2019; Vargas-Mendoza et al., 2019). Finally, genetic factors, such as specific polymorphisms, may affect individual responses to these cognitive benefits from aerobic exercise (Sarzynski et al., 2017).

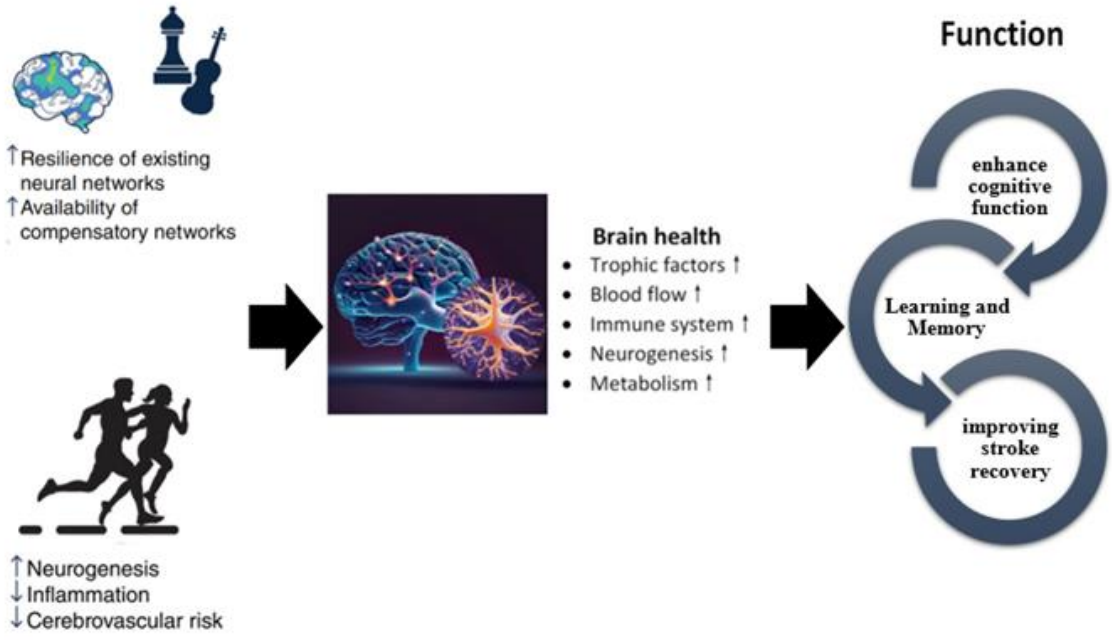

Figure 1. Enhancing brain health through cognitive and physical activities.

Impact of resistance/strength training on brain structure, function, and cognition

Resistance or strength training enhances brain structure, function, and cognition by activating cellular pathways that boost muscle health. Resistance training through the activation of PGC-1, reduces inflammation, muscle cell death, and oxidative stress, supporting cellular longevity (Wenz et al., 2009).

There is a documented link between muscle strength and cognitive health, as increased muscle power, particularly in the lower body, correlates with improved cognitive function and brain structure (Herold et al., 2019; Nakamoto et al., 2012). Resistance training may thus help mitigate age-related declines in both physical and cognitive health. According to the neurotrophic hypothesis, resistance training boosts levels of brain-derived neurotrophic factor (BDNF), promoting structural and functional brain changes that enhance cognition (Basso & Suzuki, 2017). Recent studies show that a 12-week, moderate-intensity strength training program increases levels of myokines like BDNF, irisin, IGF-1, and CATB, which further support brain health and cognitive performance (Wang et al., 2024).

Muscle-brain crosstalk: The role of myokines and metabolites

Muscle-brain crosstalk refers to the interaction between muscles and the brain through muscle-derived factors, particularly myokines, released during physical activity (Delezie & Handschin, 2018). Myokines, such as irisin, are hypothesized to facilitate neurogenesis and cognitive processing by stimulating brain regions associated with learning and memory. This bidirectional communication supports the idea that muscle activity directly contributes to brain health, reinforcing the cognitive advantages of exercise (Furrer & Handschin, 2024) (see Figure 2).

Neurotrophic factors

Biologically active BDNF functions as a dimer, comprising two identical peptide chains connected through noncovalent interactions. The precursor form, proBDNF, accumulates in both dendrites and axons, undergoing cleavage either inside or outside the cell to form the mature protein (Dadkhah et al., 2023). BDNF is linked to greater hippocampal volume and improved memory, but its expression in the brain declines with age, raising susceptibility to neurodegenerative diseases (Webster et al., 2006). Aging causes damage to muscle and nerve tissues, correlating with declines in memory and hippocampal neurogenesis. Exercise induces beneficial stress, or hormesis, which promotes brain repair, with BDNF being crucial for recovery. In older adults, long-term exercise has been shown to increase BDNF and expand hippocampal regions. BDNF is also produced in skeletal muscle, where it aids fat metabolism and can cross into the brain. However, research is still exploring whether muscle-derived factors directly stimulate BDNF production in the brain (De la Rosa et al., 2019).

Irisin

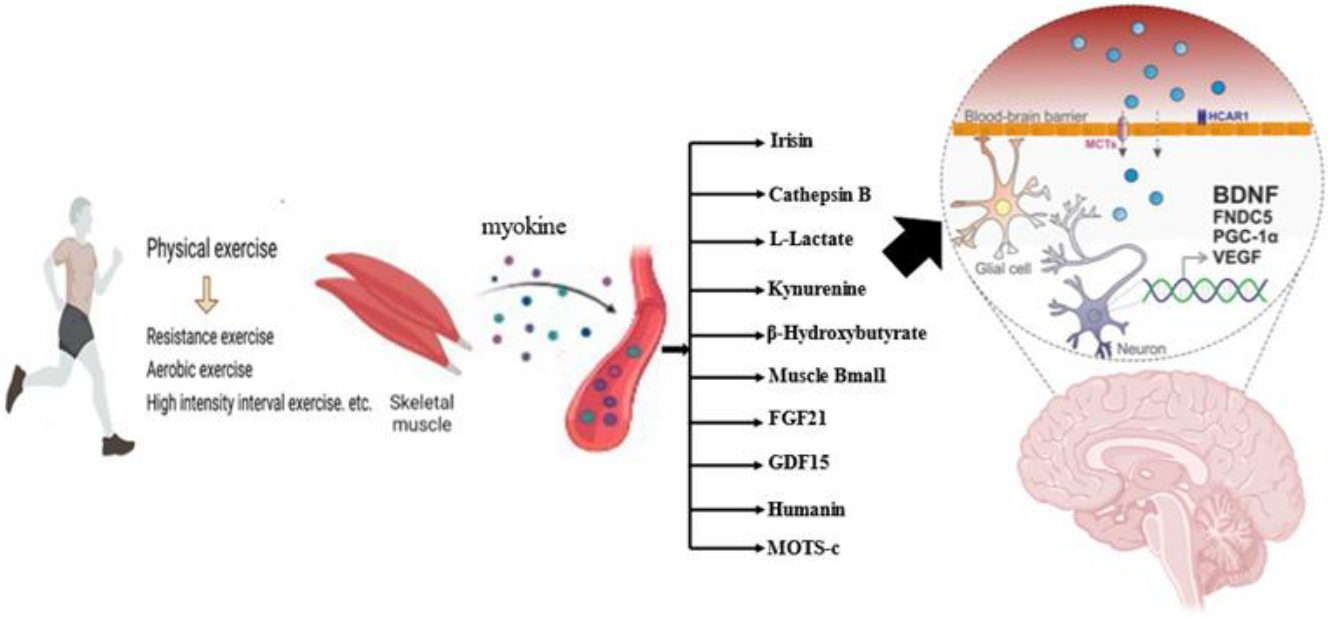

Figure 2. Neuroprotective effects of exercise via circulating myokines. Exercise stimulates the upregulation of BDNF, FNDC5, PGC-1α, and VEGF, promoting the release of various myokines, including irisin, cathepsin B (CTSB), lactate, kynurenine, β-hydroxybutyrate, Bmal1, FGF21, GDF15, humanin, and MOTS-c, all of which contribute to exercise-induced neuroprotection.

Irisin

Irisin, a myokine primarily released by skeletal muscle during exercise, plays a key role in supporting both muscle and brain health (Han et al., 2023). Exercise stimulates irisin production by activating transcription regulators like CaMK, AMPK, and P38-MAPK, which in turn stimulate FNDC5 and PGC-1α, the primary pathways involved in irisin synthesis (Aldiss et al., 2018). In the brain, FNDC5—closely related to irisin—supports neuron development and appears to play a critical role in cognitive function. Research shows that FNDC5 levels increase in the hippocampus with exercise, which is associated with an upregulation of BDNF, a protein crucial for learning and memory (Hashemi et al., 2013). Evidence suggests that muscle-derived FNDC5 may cross the blood-brain barrier, enhancing BDNF expression in the hippocampus. This pathway is thought to link exercise with improved brain function and cognitive health (Pedersen, 2019). Recent studies further suggest that FNDC5 and irisin may influence synaptic function and memory, offering therapeutic potential for neurodegenerative conditions like Alzheimer's disease (Lourenco et al., 2019).

Cathepsin B

Cathepsin B (CTSB) and BDNF are key peripheral factors in cognitive health (Pareja-Galeano et al., 2015). CTSB, a myokine produced during exercise, can cross the blood-brain barrier and stimulate the production of doublecortin and BDNF, supporting cognitive function. Studies indicate that exercise elevates CTSB levels in the hippocampus and plasma, suggesting CTSB's role in mediating exercise-induced cognitive benefits (Moon et al., 2016). Some studies report that increased CTSB from high-intensity exercise correlates with improved cognition, though further research is needed to clarify CTSB's precise role in cognitive enhancement through exercise (Gökçe & Gün, 2023).

L-Lactate

Lactate is a metabolite produced from pyruvate during intense exercise, particularly under low oxygen conditions (Wahl et al., 2018). lactate considered a waste product, is now recognized for its role as an energy source and signaling molecule that can enhance cognitive function. It promotes the expression of vascular endothelial growth factor (VEGF)-A in the brain, which supports neurogenesis and angiogenesis, especially following brain injuries (Zhou et al., 2018). Lactate enters the brain via monocarboxylate transporters (MCTs) and activates receptors that supports neuronal activity and cognitive learning linked to hippocampal function. Accumulation of lactate in the bloodstream during exercise may boost neurogenesis and cognitive learning associated with the hippocampus (Lev-Vachnish et al., 2019). Additionally, higher levels of aerobic exercise, especially during high-intensity interval training (HIIT), are correlated with increase BDNF expression, further enhancing cognitive function (Marquez et al., 2015).

Lactate's transport across the blood-brain barrier, particularly via MCT-2 expressed in astrocytes, allows it to function similarly to neurotransmitters. Its ability to stimulate BDNF expression involves activation of specific signaling pathways, which contribute to improved neuronal plasticity (El Hayek et al., 2019). These mechanisms may explain the cognitive benefits of exercise for individuals with mood disorders, dementia, and Alzheimer's disease (Sá Filho et al., 2024).

Kynurenine

Kynurenine (KYN) and its derivatives are recognized for their significant influence on the CNS and have been linked to a range of psychiatric and mental health disorders. Approximately 60% of KYN in the CNS is sourced from peripheral circulation, transported across the BBB, while the rest is synthesized locally (Cervenka et al., 2017). The metabolism of KYN is mainly regulated by kynurenine aminotransferases (KATs), which convert KYN to KA, and kynurenine-3 monooxygenase (KMO), which produces QA. This metabolic pathway is initiated by the conversion of tryptophan (TRP) into KYN, a process affected by chronic inflammation that can lower serotonin levels, potentially leading to mood disorders (Joisten et al., 2020). Research indicates that exercise positively impacts the kynurenine pathway, suggesting a link between physical activity and mental health. Exercise may increase KA levels through mechanisms involving PGC-1α, which enhances KAT gene expression in skeletal muscle (Allison et al., 2019; Baxter-Parker et al., 2019; Kim et al., 2015; Mudry et al., 2016). Additionally, the interplay between brain-derived neurotrophic factor (BDNF), exercise, and the kynurenine pathway suggests that physical and cognitive activities could enhance cognitive function by influencing these biological mechanisms. While irisin and KA correlate positively with physical, cognitive, and social activities, neurotoxic metabolites from the kynurenine pathway are negatively associated with these activities (Agudelo et al., 2014; Kuester et al., 2017; Marques-Aleixo et al., 2021).

β-Hydroxybutyrate

Ketone bodies, including β-hydroxybutyrate (BHB) and acetoacetate, are produced in the liver from fatty acids and play a crucial role as an energy source during fasting, dieting, and intense exercise. Numerous studies have highlighted the neuroprotective properties of ketone bodies in neurodegenerative disorders and neuronal function, particularly during epileptic episodes (Wang et al., 2021).

Research indicates that ketones may function as growth factors for hippocampal neurons and offer protection against mitochondrial dysfunctions linked to AD. The BHB has also been

recognized to enhance and restore memory functions (Dahlgren & Gibas, 2018). During exercise, ketones stimulate BDNF production in the hippocampus through the FNDC5-PGC-1α pathway, improving cognitive performance (da Fonseca, 2024). This process is aided by an increase in MCT2 transporters, which boost BDNF levels, receptor activity, and synaptic transmission (Takimoto & Hamada, 2014). Ketones may positively impact cognitive health, especially for individuals with neurodegenerative diseases or depression. These individuals could benefit from BHB's ability to stimulate BDNF, which supports brain function (Sleiman et al., 2016). Overall, ketones influence brain energy metabolism, mitochondrial respiration, and BDNF expression, suggesting potential therapeutic roles in conditions like Alzheimer's and Parkinson's disease (Marosi et al., 2016).

Muscle Bmal1

The molecular clock genes, including CLOCK and BMAL1, regulate circadian rhythms by driving the expression of Per and Cry genes across cells (Wolff & Esser, 2019). These rhythms impact critical bodily functions like metabolism, sleep, and nutrient processing, and notably impacted by disorders related to dementia (Martin et al., 2023). Altered BMAL1 methylation patterns in AD suggest that clock gene changes may contribute to cognitive decline (Cronin et al., 2017). Additionally, disruptions to circadian rhythms can impair autophagy—a process essential for slowing cognitive decline and reducing amyloid-beta plaque buildup, a hallmark of AD. Environmental factors, like sleep disturbances, affect autophagy-related proteins in the hippocampus, potentially impairing memory and cognitive functions (Maiese, 2020). BMAL1 and PER1 are critical for brain health, with PER1 playing a neuroprotective role by promoting autophagy (Rami et al., 2017). Circadian rhythms influence the mTOR pathway, which is linked to neurodegeneration and aging, and melatonin helps regulate this pathway to protect cognitive function. Lower mTOR activation can influence circadian rhythms and may protect cognitive function by modulating autophagy (Jenwitheesuk et al., 2014; Ramanathan et al., 2018). SIRT1 and mTOR's modulation is crucial for cognitive health, as imbalances in their activity affect neuron development and maturation (Liu et al., 2014). Exercise, particularly moderate aerobic exercise, particularly in the early recovery stages following a stroke, has been found to regulate skeletal muscle clock genes, thereby influencing physical performance (Mai Li et al., 2024). Exercise's timing is significant for molecular responses involving mTORC1 and PGC-1α pathways, which support endurance and mitochondrial function in skeletal muscle (Ramanathan et al., 2018; Wolff & Esser, 2019).

FGF21

Fibroblast growth factor 21 (FGF-21) is a member of the fibroblast growth factor superfamily and is produced in response to various stressors, including exercise, fasting, and mitochondrial dysfunctions. It is considered a potential therapeutic target for metabolic disorders such as obesity, insulin resistance, and type 2 diabetes (Ji et al., 2024). Research indicates that circulating FGF-21 promotes the proliferation of oligodendrocyte precursor cells, a process that requires the co-receptor β-Klotho for effectiveness. However, under normal conditions, FGF-21 has limited access to the CNS, as its levels in cerebrospinal fluid (CSF) are approximately 60% lower than in peripheral blood. Despite this, FGF-21 can cross the BBB and plays a supportive role in myelination processe (Zhang et al., 2023). Moreover, FGF-21 influences the expression of the VEGF2 receptor, which regulates the migration of oligodendrocyte precursor cells, thus indirectly affecting oligodendrocyte development and remyelination. While the precise role of FGF-21 in enhancing brain plasticity remains unclear, its neuroprotective effects on neurons have been well established (Kim et al., 2023).

GDF15

Exercise significantly stimulates the release of myokines, including mitokines, from active muscles in response to mitochondrial stress caused by muscle contractions. Among these, Growth Differentiation Factor 15 (GDF15) levels increase following both aerobic and resistance exercises (Johann et al., 2021). Research shows that GDF15 rises during the recovery period; for instance, after one hour of intense cycling, levels increased from 0.22 ng/mL to 0.3 ng/mL immediately post-exercise and reached 0.35 ng/mL after three hours of recovery (Kleinert et al., 2018).

The GDF15 gene expression is regulated by the p53 protein, which initiates its transcription in response to stressors like hypoxia and inflammation, similar to the regulation of other proteins like irisin and CSTB. Additionally, the expression of FGF21 is modulated by PGC-1α. One study has associated GDF15 with age-related cognitive decline and an increased risk of dementia (Kleinert et al., 2018). Notably, FGF21 can cross the BBB, though the exact mechanisms of this process remain unclear (Burtscher et al., 2021).

Humanin

Humanin (HN) is a short peptide composed of 21 or 24 amino acids, found in various organs including the heart, kidneys, liver, skeletal muscle, and brain (Atakan et al., 2024). It functions primarily at the cellular level but is also present in plasma and cerebrospinal fluid. The specific tissues contributing to circulating humanin levels and the mechanisms of its secretion are not fully understood (Karachaliou & Livaniou, 2023).

Research highlights the protective role of humanin against cognitive dysfunction and neurological disorders, particularly Alz-

-heimer's disease (AD).

One proposed mechanism is the inhibition of cytochrome c release, which interacts with pro-apoptotic proteins such as Bim, Bid, and Bax. Humanin has been shown to mitigate cognitive dysfunction and reduce inflammation associated with markers like IBA-1, IL-6, and IL-10 (Coradduzza et al., 2023).

Exercise enhances brain function by increasing blood flow and cellular respiration, leading to the upregulation of neuroprotective proteins such as brain-derived neurotrophic factor (BDNF) and humanin. These proteins are critical for synapse development, plasticity, and neuronal survival under stress. A decline in their levels is linked to the progression of AD. Therefore, reduced humanin levels may indicate mitochondrial dysfunction in AD, suggesting that increasing humanin through physical activity could be a non-pharmacological strategy for combating AD (Delgado-Peraza et al., 2023).

MOTS-c

MOTS-c is a peptide encoded by the short open reading frame of the mitochondrial 12S rRNA gene. MOTS-c is expressed in various tissues, such as skeletal muscle and the brain, and is also found in plasma (Zempo et al., 2021). This peptide activates AMP-activated protein kinase (AMPK) and acts as an insulin sensitizer (Mohtashami et al., 2022). Both Humanin and MOTS-c play crucial roles in reducing chronic inflammation and cognitive decline, contributing to neuroprotection, metabolic regulation, cellular signaling, and apoptosis inhibition. Research in mice has demonstrated that MOTS-c treatment stimulates AMPK activation in skeletal muscle, a key regulator associated with exercise, by increasing cellular levels of AICAR (an AMPK agonist) and GLUT4 (Mengfan Li et al., 2024; Mohtashami et al., 2022).

Furthermore, Jiang et al. (2021) found that MOTS-c therapy enhances object and spatial recognition memory formation by promoting AMPK phosphorylation, reducing the activation of astrocytes and microglia, and lowering the production of pro-inflammatory cytokines (Jiang et al., 2021).

Conclusion

This review examined the critical role of physical and cognitive activities in supporting brain health in older adults. Engaging in physical activity, particularly aerobic exercise, is essential for preserving the structural integrity of neurons and maintaining overall brain volume. In contrast, cognitive activities enhance the functionality and adaptability of neural circuits. A healthy neuronal structure is fundamental for individuals to fully engage in and reap the benefits of cognitive training, while cognitive functions, especially executive processes, can promote adherence to physical activity programs.

A significant mechanism underlying these benefits is the muscle-brain crosstalk, which involves various signaling molecules known as myokines produced by skeletal muscles. These myokines are crucial for enhancing cognitive functions, memory, and motor coordination. Exercise influences the expression of myokines, facilitating both autocrine regulation of muscle metabolism and paracrine/endocrine regulation of distant organs. While the specific bioactivity of myokines remains to be fully characterized, a deeper understanding of their secretion and release from muscles—and their effects on the brain—could elucidate the connection between muscle activity, exercise, and brain function. This knowledge may also lead to the development of small compounds derived from myokines as potential treatments for neurodegenerative diseases.

Data sources

To gather relevant literature for this narrative review, several databases were systematically searched, including PubMed, Google Scholar, and Web of Science. The following keywords were used in various combinations to ensure comprehensive coverage of the topic: "brain health," "older adults," "exercise," "muscle-brain crosstalk," "neuroplasticity," "aerobic exercise," "cognitive function," "myokines," "Lactate," "Irisin," "Cathepsin B," "Kynurenine," "Hydroxybutyrate," "Muscle Bmal1," "FGF21," "GDF15," "Humanin," "MOTS-c," and "BDNF." Searches were limited to peer-reviewed articles published in English. Additionally, reference lists of relevant studies were reviewed to identify any additional sources not captured in the database searches.

What is already known on this subject?

Engaging in physical activity, particularly aerobic exercise, is essential for preserving the structural integrity of neurons and maintaining overall brain volume.

What this study adds?

We consider how exercise can promote brain health in aging populations through new mechanisms such as muscle-brain crosstalk.

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Compliance with ethical standards

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