Lifestyle Medicine and Preventive Neurology

Cyrus Safaeipour, BS, Dean Sherzai, MD, PhD, Bashir Zikria, MD

Exercise and Brain Health: Expert Review

Abstract: *Preserving brain health is essential to maintaining quality of life and cognitive function with age. Exercise plays an essential role. Aerobic exercise such as running and cycling can enhance brain plasticity through increasing gray matter volume in the cerebellum and temporal lobe, as well as the density of connections in the brain's frontal and motor areas via upregulating brain-derived neurotrophic factor (BDNF) and serotonin systems. Anaerobic exercise, such as weightlifting, primarily increases gray matter volume in the basal ganglia and increases the density of connections in the posterior lobe of the cerebellum. In midlife, aerobic exercise can increase white matter integrity and cortical thickness in primary motor and somatosensory areas, while in older age it improves specific markers of cognitive function, such as episodic memory. With regards to neurodegenerative diseases, aerobic exercise has been linked to improved memory performance and reduced hippocampal atrophy in Alzheimer's disease. In Parkinson disease, aerobic exercise has shown to reduce brain atrophy, improve motor function and cognitive control, while anaerobic exercise improves motor performance and information processing. Overall, both aerobic and anaerobic exercises are integral and complementary to preserving brain health through effects on cognitive function and brain structure.*

Keywords: cognitive preservation; brain health; cognitive function; aerobic exercise; anaerobic exercise

"Long-term regular exercise reduces the likelihood of developing cognitive impairment and dementia."

Introduction

Why Brain Health Matters

Brain health is impacted by many variables but is imperative to neuroplasticity, cognitive function, and mental well-being. How the brain functions in sensory, cognitive, social-emotional, behavioral, and motor domains allows one to live to their full potential and is an indicator of brain health.[1] Enhancing brain health can reduce incidence of neurological disease and improve overall quality of life via improving brain structure and function.[1]

Cognitive function is impacted by brain health, and can decline due to age-related changes in synaptic connections fundamental to learning and memory.[2] Lifestyle interventions, such as physical activity, can help preserve brain health and improve cognitive function through enhancing synaptic plasticity, neurogenesis, and cerebral perfusion.[3,4] The American Heart Association encourages the management of modifiable risk factors such as hypertension, diabetes, and physical inactivity as ways to preserve brain health and prevent cognitive impairment.[5]

Mental well-being, such as preventing onset of depression or anxiety, is impacted by brain health. For instance, regular physical exercise has shown to improve symptoms of depression and anxiety, enhance sleep quality, and improve overall quality of life.[6]

DOI: 10.1177/15598276251415530. Boston University Chobanian and Avedisian School of Medicine, Boston, MA, USA (CS); Charles R. Drew University of Medicine and Science, Los Angeles, CA, USA (DS); and The Johns Hopkins University School of Medicine, Baltimore, MD, USA (BZ). Address correspondence to: Cyrus Safaeipour, BS, Boston University Chobanian and Avedisian School of Medicine, 72 E Concord St, Boston, MA 02118, USA. e-mail: cyrussaf@bu.edu.

These benefits are mediated through the release of neurotransmitters such as dopamine and serotonin, which regulate mood, as well as reductions in oxidative stress and neuroinflammation.[7,8]

Furthermore, neuroplasticity, the brain's ability to recognize itself and form new connections, is pivotal to brain health by allowing the brain to recover from injuries and adapt to new experiences. Neuroplasticity has also been shown to be impacted by diet and physical exercise.[4,9]

Recognizing how vital brain health is for quality of life, many are eager to find ways to preserve and enhance it. Thus far, lifestyle factors, such as exercise, have been shown to be a promising method to improve domains of brain health, such as cognitive function and mental well-being. Exercise can improve cognitive function through promoting the release of growth factors such as BDNF, which enhances synaptogenesis, angiogenesis, and neurogenesis, directly impacting learning and memory.[7,8,10,11] Exercise also improves cerebral blood flow and mitochondrial formation, both necessary for cognitive health.[4,8,12-17]

Optimal brain health has been correlated with regular, moderate-intensity physical exercise, whether aerobic, anaerobic or a mix of the two.[4,11,18] Significant cognitive benefits have been shown attainable with at least three sessions of 40 minutes of physical activity per week.[18]

Exercise as a Modifiable Factor

Aerobic exercise, such as running and cycling, increases heart rate and oxygen consumption. Anaerobic exercise, such as weightlifting and sprinting, depends more on stored energy in muscles rather than oxygen and is marked by high-intensity activity. Aerobic exercise has been shown to improve memory, attention, and executive function. These improvements in cognitive function are believed to be due to proven increases in prefrontal cortex thickness and hippocampal volume.[11,19,20]

Increased aerobic exercise has also shown to improve mental well-being through increasing release of dopamine and serotonin in the brain, which reduce neuroinflammation and reduce symptoms of depression and anxiety.[21] Additionally, aerobic exercise enhances neuroplasticity, specifically neurogenesis and synaptic plasticity in the hippocampus, increased neurotrophic and vascular factors that support neuronal growth and survival.[22]

Anaerobic exercise can similarly be used to modify brain health. It can improve aspects of cognitive function such as reaction time, although impact on other areas of cognitive function are not as apparent as aerobic exercise.[23] In terms of mental well-being, anaerobic exercise has shown efficacy in reducing stress and anxiety, although the mechanisms are not as well delineated as aerobic exercise.[24] Additionally, anaerobic exercise improves neuroplasticity, particularly in the basal ganglia which is involved in motor control and procedural learning.[24]

Purpose

This review highlights the importance of exercise as a neuroprotective strategy due to the body of literature that shows its ability to enhance cognitive function, mental well-being, and neuroplasticity. Exercise can improve memory, attention, and executive function through upregulation of neurotrophic and growth factors such as insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF), which support neurogenesis and synaptic plasticity in the hippocampus.[25-27]

Exercise is also incredibly useful in improving mental health due its ability to increase dopamine and serotonin neurotransmitter release in the brain, improving mood and anxiety. It also reduces neuroinflammation and oxidative stress that can worsen mental health outcomes.[7,8] Exercise supports cognitive resilience throughout life by also increasing neuroplasticity. Thus, the brain can better organize itself and form new neural connections when adapting to new experiences, or recovering from injury.[28-30] Exercise is also neuroprotective against neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Through increasing neuronal survival, neurogenesis, angiogenesis, and reducing neuroinflammation and oxidative stress, exercise can delay brain aging and preserve memory and cognition.[31,32]

Overview of Brain Health and Cognitive Function

Definition of Brain Health

Brain health is multifaceted and has many contributing factors, such as cognitive, emotional, and motor health.[33,34] Cognition is critical to brain health, and is identified by processes such as memory, attention, and executive function. These cognitive processes are crucial for everyday life and can be preserved and enhanced through activities such as physical exercise, education, and social engagement.[35,36]

Memory is another critical contributing factor to cognition that can be preserved and improved with lifestyle interventions, such as physical exercise. Regular physical exercise promotes neurogenesis and synaptic plasticity in the hippocampus, a brain area key for memory.[2,37] Mental health is also necessary for brain health, is influenced by cognitive function and neuroplasticity, and is positively modified by physical exercise and social engagement. These modifiers help reduce symptoms of depression and anxiety.[35,37]

Neurogenesis, BDNF, and neuroplasticity play crucial roles in maintaining aspects of brain health, such as memory and attention. Neurogenesis allows for new connections to be made in the brain, such as in the hippocampus for storing memory.[38,39] BDNF is a neurotrophin that supports the survival, growth, and differentiation of neurons. It improves synaptic plasticity and is important in learning and memory. It brings about these changes through signaling via its TrkB receptor, and can be modulated by physical activity, stress, and environment.[38-41] Increased neuroplasticity supported by neurotrophic signaling, improved metabolic function, and reduced neuroinflammation is also protective against neurodegenerative diseases and symptoms of depression.[38,42]

Importance of Physical Activity

Neuroimaging evidence shows that brain structure and function change in response to regular physical activity.[6,8] Physical activity improves memory, attention, executive function, processing speed, and academic performance. These improvements are thought to be due to exercise-induced neurogenesis in the hippocampus facilitated by neurotrophic and vascular factors that support neuronal growth and synaptic remodeling.[8] While physical exercise promotes brain health, sedentary behavior has shown to negatively impact brain health by reducing cognitive function, brain volume, and even cortical thickness in regions such as the medial temporal lobe, critical for memory.[43-45]

Mechanisms Linking Exercise to Brain Health

Aerobic Exercise and Brain Health

Cardiovascular and Metabolic Effects. Aerobic exercise increases cerebral blood flow, which increases oxygen and nutrient delivery to brain areas critical for memory and learning, such as the hippocampus.[46,47] Increasing the flow of oxygen and nutrients to the hippocampus allows it to increase in volume, leading to improvements in spatial memory and overall cognitive function. A randomized clinical trial, for instance, showed that regular aerobic exercise specifically increased anterior hippocampus size, reversing age-related volume loss and improving memory.[46] These hippocampal changes are mediated by elevations in growth factors such as insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF), which promote neurogenesis, angiogenesis, and synaptic remodeling.[46,48,49]

Neurochemical Changes. Positive effects of aerobic exercise arise from coordinated neurochemical, vascular, and anti-inflammatory responses that enhance synaptic strength. Growth factors including IGF-1 and VEGF promote neuronal survival, differentiation, and angiogenesis, and their levels rise with aerobic activity.[15,50-53] These changes are particularly evident in the hippocampus, where neurogenesis and synaptic remodeling improve spatial memory and cognitive function.[51-53] The increased synaptic plasticity in these brain areas allows for improved cognitive resilience and recovery after brain injury, which leads to better executive function, attention, processing speed, and cognitive performance.[15,50-53] Neurochemicals important to maintaining good mental health, such as dopamine and serotonin, are also released more in response to regular aerobic exercise.[15,50-53]

Reduction in Neuroinflammation

Reduction of Oxidative Stress. The primary way aerobic exercise reduces oxidative stress in the brain is by upregulating expression of antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx), which neutralize reactive oxygen species. These specific enzymes are upregulated via activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, which increases expression of antioxidant response elements (AREs) like heme oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase 1 (NQO1).[54-56]

Reduction of Inflammation. Aerobic exercise decreases brain inflammation by reducing the activation of resident immune cells in the brain—microglia and astrocytes—leading to decreased production of pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and tumor necrosis factor-alpha (TNF-α). Exercise also inhibits other key regulators of inflammation, namely, the mitogen-activated protein kinase (MAPK), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathways.[57-59] The NF-κB pathway is modulated through the release of irisin, a myokine which reduces expression of inflammatory mediators.[59]

Anaerobic Exercise and Brain Health

Impact on Muscle and Brain Connection. Anaerobic exercise, including resistance training, improves brain health by stimulating the release of myokines such as irisin and cathepsin B, which cross the blood–brain barrier and activate neurotrophic and vascular pathways that support synaptic plasticity and neurogenesis.[60,61] Anaerobic exercises such as strength training also improve coordination and motor skills through increasing corticospinal excitability and increasing synaptic efficacy. These changes lead to better motor control and cognitive performance. Strength training also improves inter-muscular coordination, which stabilizes sensorimotor coordination and improves the execution of complex motor tasks.[14,62,63]

Hormonal Responses. Anaerobic exercise changes levels of neurotrophic factors and hormones, such as insulin-like growth factor 1 (IGF-1) and testosterone. Changing levels of these factors can improve brain plasticity and cognitive performance. For instance, strength training increases IGF-1 production by the liver. IGF-1 can then cross the blood–brain barrier and go to the hippocampus, where it promotes neurogenesis and synaptic plasticity. Simultaneously, the increased levels of IGF-1 facilitate neuronal growth and modulate synaptic transmission, contributing to improved learning and memory.[14,64]

The sex hormone testosterone is also neuroprotective, increases with anaerobic exercise, and improves synaptic plasticity and neurogenesis. The effects of testosterone are particularly helpful in combating age-related cognitive decline.[65]

Potential for Reducing Anxiety and Depression. Anaerobic exercises also improve mood and mental health through their impact on neurotransmitters such as serotonin and dopamine. Meta-analyses and systematic reviews have shown that anaerobic exercises such as resistance training significantly reduce symptoms of depression and anxiety. These protective effects help preserve cognitive function.[66-69]

Aerobic Exercise—Cognitive and Emotional Benefits

Memory-Linked Hippocampal Changes

Aerobic exercises such as running and cycling improve memory and learning by causing changes in hippocampal volume via the same mechanisms described in the section, "Mechanisms Linking Exercise to Brain Health". For instance, a randomized controlled trial showed that hippocampal volume can increase by 2% in response to regular aerobic exercise. The increase in hippocampal volume is correlated with improved spatial memory and reversal of age-related volume loss.[46]

Interestingly, aerobic exercise's impact on hippocampal volume is greatest during adolescence, with the greatest effect on the hippocampal head, specifically the CA1 region and the dentate gyrus/CA3 subregion. Increased volume of the CA1 region is correlated with improved verbal and spatial learning. Increased volume of the dentate gyrus/CA3 subregion has shown to improve mnemonic discrimination, which helps in learning and memory.[70,71]

Cognitive Flexibility and Attention

Aerobic exercise has been shown to improve cognitive flexibility and attentional control through enhancements in executive function. Executive functions, including attention, self-control, and planning, are strengthened in part due to exercise-induced increases in neurotrophic signaling and synaptic plasticity within brain regions involved in cognition.[72,73] Additionally, executive functions such as cognitive flexibility and attention are improved with increased cerebral blood flow, nutrient, and oxygen delivery to the brain during and after aerobic exercise.[49,53]

Enhancement in Processing Speed

Aerobic exercise enhances the brain's ability to process information quickly and efficiently through improvements in cognitive flexibility, attentional control, and overall executive function. Specifically, aerobic exercise can improve aspects of cognitive flexibility such as switching between tasks, facilitating task-set reconfiguration and maintaining a task in working memory, leading to improved performance when task-switching.[74-76] Aerobic exercise's enhancement of cerebral blood flow to the brain also leads to faster response times and accuracy in tasks requiring inhibitory control.[77-79] These improvements in information processing speed, attention, and executive function are largely brought about via the same mechanisms described in the section, "Mechanisms Linking Exercise to Brain Health".[13,80]

Improvement in Working Memory

A systematic review and meta-analysis demonstrated that aerobic exercise significantly improves working memory in middle- and older-age adults.[80] These improvements are believed to be due to mechanisms and hormonal changes described in the section, "Mechanisms Linking Exercise to Brain Health".[16,77,80,81] Effective problem-solving and decision-making require inhibitory control and cognitive flexibility to absorb, adapt, and make decisions. These cognitive domains have been shown to improve with acute aerobic exercise.[12,82]

Mood Regulation and Neurotransmitters

The two main neurotransmitters that impact mood regulation and stress are serotonin and dopamine. Aerobic exercise can increase the release of both serotonin and dopamine, leading to improved mood regulation and stress reduction through different pathways. Mechanistically, dopamine increases production of BDNF, which also leads to increased TrkB receptor activity. Serotonin, however, increases synaptic plasticity in key integration centers of the brain, such as the anterior cingulate cortex (ACC). Both pathways promote feelings of happiness and well-being and are protective against symptoms of depression.[66,83]

Cortisol Regulation

Through improved regulation of the hypothalamic-pituitary-adrenal (HPA) axis, aerobic exercise can lessen feelings of stress by decreasing serum cortisol levels. Regular aerobic exercise strengthens negative feedback on the HPA axis, which allows for finer control of cortisol release in response to stressors, and lower baseline cortisol levels. For instance, a study showed that participants who engaged in aerobic exercise had significantly reduced cortisol levels in response to stress, indicating improved HPA axis modulation.[84] Regular aerobic exercise also increases adrenal gland sensitivity to stress, leading to more rapid and efficient cortisol response to stressors, which decreases chronic exposure to elevated cortisol levels.[85]

Anaerobic Exercise and Specific Brain Functions

Coordination and Brain Connectivity

Resistance and strength training exercises improve motor skills and neuromuscular coordination through enhancing coordination between muscle groups and changing brain chemistry. For instance, strength training improves inter-muscular coordination and increases corticospinal excitability, leading to greater neurocognitive control. These changes also allow for improved performance on cognitive tasks requiring fine motor skills. These improvements allow the brain to more efficiently process and respond to motor information.[63] Improvements in cognitive control and neuromuscular coordination during motor skills are also partly due to neurochemical changes described in the section, "Mechanisms Linking Exercise to Brain Health", which support neurogenesis and synaptic plasticity during learning of motor skills.[10]

Strength Training and Mental Health

Anaerobic exercises, such as resistance training, can significantly reduce symptoms of depression and anxiety in different populations and settings. For instance, a study showed that low-to-moderate intensity resistance training (<70% 1 repetition maximum) reliably decreases anxiety.[69,86] Moreover, resistance training can also improve disorder-specific symptoms, such as intolerance of uncertainty, distress tolerance, and anxiety sensitivity in patients with anxiety disorders.[69,86] With regards to depression, a meta-analysis highlighted how resistance exercise training, through regulating neurotransmitter and neurotrophic factors, can reduce symptoms of both depression and anxiety.[87] Furthermore, The American College of Sports Medicine endorses resistance training as a treatment to substantially reduce symptoms of anxiety and depression across all age groups.[88]

While both anaerobic and aerobic exercises have shown to improve mental health outcomes, they can do so through targeting different aspects of stress reduction and mood regulation. Aerobic exercises such as running and cycling, for instance, enhance mood and reduce stress primarily by increasing release of the neurotransmitters dopamine and serotonin, and reducing serum cortisol levels.[89] Anaerobic exercises such as resistance training, in contrast, have more of an impact on cognitive control via neuromuscular adaptations, enhancing coordination and motor skills, which are linked to cognitive function.[69] Depending on the mental health outcome desired, one can vary the amount of aerobic and anaerobic exercise they perform.

Cognitive Behavioral Changes

Anaerobic exercises, such as strength training, can improve self-efficacy, cognitive control, and mental well-being. Resistance training with weights, for instance, allows individuals to feel a sense of accomplishment and mastery as they progress in using heavier weights and as they see their muscles increase in size. These physical changes over time have been shown to improve self-efficacy, mental health outcomes, and ability to regulate stress during adversity.[10]

Additionally, strength training enhances cognitive control through improving neuromuscular coordination and executive function. Improvements in cognitive functions such as attention, processing speed, and inhibitory control, have been correlated to neuroplastic changes within the brain during resistance exercise.[10] These refinements have been shown to be mediated by growth factors and hormonal changes described in the section, "Mechisms Linking Exercise to Brain Health".

Exercise and Neurodegenerative Diseases

Alzheimer's Disease and Dementia

Protective Effects of Aerobic Exercise. Aerobic exercise can slow cognitive decline through improving vascular function and preserving hippocampal volume. Hippocampal volume is correlated with learning and memory, and has been shown to increase in response to regular aerobic exercise via neurochemical changes described in the section, "Mechanisms Linking Exercise to Brain Health".[46] Specifically, a randomized clinical trial showed that aerobic exercise training increased the volume of the anterior hippocampus by 2%, decreasing age-related volume loss and improving spatial memory.[46]

Additionally, regular aerobic exercise improves oxygen and nutrient delivery to the brain by enhancing cerebral blood flow. Among individuals carrying the Apolipoprotein E4 allele—a genetic risk factor for Alzheimer's disease—a study found that aerobic exercise improved hippocampal blood flow.[90] Another study showed improved blood flow specifically to the anterior cingulate cortex, an area associated with improved memory function.[91] Regular aerobic exercise has also shown to increase cognitive scores among people with dementia and mild cognitive impairment. For instance, a randomized controlled trial showed that aerobic exercise reduced hippocampal atrophy and improved memory performance.[81]

Potential Benefits of Strength Training. Resistance training can reduce brain atrophy and increase brain connectivity, preventing overall cognitive decline. Data from the Study of Mental Activity and Resistance Training (SMART) trial suggests that resistance training protects hippocampal subfields, specifically the left subiculum, left CA1 and dentate gyrus, for at least one year post-intervention. These hippocampal subfields are prone to atrophy in Alzheimer's disease, and their preservation also led to long-term cognitive function improvements in the studies' participants, highlighting the link between preserving brain structure and function.[92] In their narrative review, Nicola et al present evidence from randomized controlled trials that resistance exercise increases gray matter volume in the hippocampus and parahippocampal gyrus, a protective mechanism against AD.[93] Furthermore, they show that these neuroprotective effects occur in a dose–response relationship in adults already experiencing cognitive decline.[93]

Resistance training also improves functional brain connectivity, specifically global cognition and gray matter in the posterior cingulate, a region necessary for cognitive control and memory. Studies show how improvements in these areas correlate with increased functional connectivity between the hippocampus and surrounding brain regions, highlighting how resistance training increases the density of functional networks.[94] Additionally, with regards to Alzheimer's disease, studies with older women demonstrate that resistance training twice per week significantly decreased atrophy of cortical white matter, improved memory, and executive function for over 2 years after study completion.[95] These results support resistance training as a worthwhile means of protecting the brain from age-related atrophy and decline.[95]

Parkinson's Disease

Motor Control and Aerobic Activity. Aerobic exercise can improve motor and cognitive symptoms of Parkinson's disease (PD), such as bradykinesia and memory impairment. Parkinsonian symptoms due to a deficit of dopamine in specific brain regions can be reversed with aerobic exercise-induced secretion of dopamine. For instance, aerobic exercise has been shown to significantly increase dopamine levels and function in the striatum of rat models.[96] Dopamine release in the caudate nucleus and activity in the ventral striatum has also been shown to significantly increase with aerobic exercise.[97] Mouse models of Parkinson's disease not only show improvements in motor function and striatal signaling with aerobic exercise, but also suggest aerobic exercise can regulate the extracellular signal-regulated kinase/mitogen-activated protein kinase (Erk/MAPK) signaling pathway. Regulation of the Erk/MAPK signaling pathway improves motor deficits in PD.[98]

Furthermore, the Park-in-Shape trial reported that regular aerobic exercise strengthened connectivity between the anterior putamen and the sensorimotor cortex, enhancing cognitive control.[99] Additionally, aerobic exercise promotes neuroplasticity by supporting the remodeling of neuronal connections in brain regions affected by Parkinson's disease, leading to improvements in motor and cognitive symptoms.[100]

Role of Anaerobic Exercise. Anaerobic exercises' positive effects on muscle control and fall risk can be leveraged to protect individuals with Parkinson's disease (PD) from injury. Regular anaerobic exercise, such as strength training, can help improve force generating capacity, neural drive, and functional performance. Abilities with the greatest improvement included chest press, leg press, plantar flexion, and rate of force development, all important for performing activities of daily living.[101] Working on balance though training with instability during exercise can also decrease fear of falling in PD patients. More specifically, strength training involving high motor complexity improves scores for balance, stability, and reduces fear of falls compared to strength training alone.[102] Additionally, regular resistance exercise has been shown to improve strength, balance, sit-to-stance, and timed up-and-go in PD patients.[103] Furthermore, combining fall prevention education with regular resistance exercise can significantly decrease the rate of falls over the span of a year, highlighting its impact on preserving functional independence.[104]

Exercise Across the Lifespan

Childhood and Adolescence

Cognitive Development. Many studies have shown that aerobic exercise regimens can have positive impacts on children's memory, attention, and cognitive function. More specifically, aerobic exercise can improve adolescent executive function, working memory, inhibitory control, and cognitive flexibility. For instance, Liu et al demonstrated in their systematic review and meta-analysis that acute and chronic exercises significantly improve the aforementioned cognitive domains in adolescents.[105] A study by Li et al reviewed the impacts of exercise on academic performance and cognitive function in adolescents, arguing that memory was the domain most enhanced by regular aerobic exercise.[106] Their study also showed that academic performance is significantly improved with chronic exercise regimens.[106]

Combining physical activity with activities requiring thinking and mental processing also leads to improved cognitive function. For instance, Ferreira Vorkapic et al argues that exercise interventions that have the greatest impact on executive function are those involving team games and coordination activities, combining physical exertion with cognitive stimulation, and social interaction.[107] In terms of improved academic performance, Davis et al performed a randomized clinical trial showing improved math achievement scores and executive function in overweight children performing regular exercise.[108] Their study also suggested a neurophysiological basis for the cognitive improvements by providing preliminary evidence that exercise increased participants' prefrontal cortex activity.[108]

Adults and Older Adults

Exercise for Cognitive Preservation. Aerobic and anaerobic exercises are becoming more recognized as tools to combat age-related cognitive decline and preserve brain health in old age. Studies on regular aerobic exercise have shown that it benefits blood flow, vascular function, and neuronal growth and connections in the brain even in old age. Among older adults, those who regularly perform aerobic exercise have been shown to have better spatial memory and larger hippocampal volume. These beneficial effects have been recognized by The American College of Sports Medicine, which endorses aerobic exercise as a method to enhance executive function and brain performance through improvements in cerebrovascular regulation.[109-111]

Anaerobic exercises, such as weight training, are also beneficial for protecting memory and executive function with age. Through mechanisms described in the section, "Mechanisms Linking Exercise to Brain Health", anaerobic exercise can lead to more synaptic connections being formed and reorganized during learning tasks. These cognitive improvements during regular anaerobic exercise, or combined with aerobic exercise, have been recognized by The American College of Sports Medicine.[110-113]

Preventing Age-Related Diseases. Aerobic and anaerobic exercise can reduce the risk of developing neurodegenerative conditions such as Alzheimer's disease (AD) and dementia. For instance, a meta-analysis by Ahlskog et al highlights how elderly individuals can reduce their risk for cognitive decline and dementia with aerobic exercise.[109] Randomized controlled trials have shown that aerobic exercise regimens can increase hippocampal volume and spatial memory among seniors, and thus prevent decline in cognition.[109] Additionally, anaerobic exercises, such as weight training, lead to significant increases in BDNF, which enhances the ability of neurons to form new connections and thus form new memories while retaining old ones.[110] Remarkably, Steves et al showed that leg power in midlife is a significant predictor of cognitive aging over a 10-year period in older women, irrespective of vascular, metabolic, lifestyle, and socioeconomic confounders.[114] This association remained true in monozygotic twins with disparate leg power, indicating the effect isn't explained by genetics or environment.[114]

Clinical studies also show the beneficial effects of exercise specifically among patients with AD or at risk for dementia. For instance, Panza et al reported significant improvements in global cognition and executive function among individuals with or at risk for AD who participated in trials of regular aerobic exercise. A study by Karamacoska et al also showed significant increases in global cognition and executive function in response to regular exercise among individuals at risk for dementia.[18,115] Mechanistically, exercise preserves memory and executive function primarily through supporting synapse formation and cerebrovascular function. More specifically, levels of neurotrophic factors, such as nerve growth factor (NGF), both increase during exercise and enhance neuron survival and synapse formation. These changes are looked at more closely by Pahlavani et al, who report how aerobic exercise preserves hippocampal volume and enhances synapse flexibility, both necessary for maintaining cognitive health in old age.[59]

Recommendations and Guidelines

Optimal Types and Duration of Exercise

Suggestions for incorporating aerobic, anaerobic, or a combination of the two forms of exercise into one's exercise routine are provided by age group in Table 1, or by exercise type below:

Aerobic Exercise:

(1) **Type**: Walking, jumping rope, rowing, cycling, elliptical, swimming, and running are effective.[109,115]
(2) **Intensity**: Moderate intensity, ~3.7 metabolic equivalents (METs) recommended.[115]

Table 1.

Brain Health Exercise Dose.

Age Group	Type	Frequency/Duration	Key Benefit
Children	Aerobic + team games	≥60 min/day	Executive function, memory
Adults	Aerobic + strength	150 min/week (aerobic) + 2x/week (strength)	Memory, processing speed, mood
Older adults	Mixed + coordination	3x/week, 45-60 min each session	Dementia risk reduction, balance, mood

(3) **Frequency/Duration**: One hour, two to three times per week, is recommended.[116]

Anaerobic Exercise (Resistance Training):

(1) **Type**: Weightlifting, calisthenics, resistance bands, body weight exercises.[110,116]
(2) **Intensity**: What the individual considers moderate to high intensity, with a focus on major muscle groups, such as chest for upper body, and calf for lower body.
(3) **Frequency/Duration**: Two to three times per week for 45-60 min.[110,116]

Combined and Integrative Training:

(1) **Combined Aerobic/Anaerobic**: Regularly performing a mix of these two forms of exercise can produce greater cognitive benefits in terms of memory and executive function.[11,110,115,116]
(2) **Integrative/Coordination Training**: Incorporating cognitive tasks during exercise, and working on balance and flexibility, can further enhance cognitive benefits.[18,116]

Limitations and Future Directions

Despite the large body of evidence showing that exercise improves brain health, there are limitations that should be addressed. While several randomized controlled trials (RCTs) show the independent effects of aerobic or anaerobic exercise, there are few comparing the effects of one to the other. This lack of comparative studies makes recommending a specific exercise modality to patients with specific circumstances difficult.[3]

Additionally, outcome measures of brain health and performance tend to vary, making it difficult to compare results. Some studies also do not provide detailed information about the exercise protocols they employed. Furthermore, there's relatively little data from studies involving under-represented minorities and neurodiverse individuals, such as those with autism or ADHD, limiting the generalizability of findings to diverse populations.[3] Addressing these issues will lead to a more complete and generalizable understanding of the effects of exercise on brain health.

Gaps in the Current Literature

Further studies are needed to explore the long-term outcomes of anaerobic training, and the mechanisms behind its impact on brain health.

(1) **Quality Evidence for Anaerobic Exercise:** Compared to aerobic exercise, there are far fewer studies exploring the effects of anaerobic exercise, short- and long-term. The difference in research quantity and quality means we can be more confident about the proven health benefits of aerobic exercise, since it's been studied far more extensively and consistently. In contrast, anaerobic exercise may offer similar or complementary benefits, but the evidence base is smaller, so our certainty about its full effects is lower. Furthermore, there are fewer studies focused on identifying optimal parameters, such as frequency, duration, and intensity of anaerobic exercises needed to maximize cognitive benefits across the lifespan.[3,117]
(2) **Molecular Mechanisms:** The exact mechanism(s) behind the neuroprotective effects of anaerobic exercise are yet to be fully elucidated. Further studies should also investigate the function of neurotrophic factors and Cathepsin B. Serum levels of these neurotrophic factors are adjusted with long-term exercise, and they are correlated with increases in memory. However, the mechanism behind how these neurotrophic factors improve memory is still not clear. Furthermore, the interplay between strength training and mitochondrial function, and brain-muscle signaling should be further studied.[118,119]
(3) **Epigenetics and miRNA:** Exercise may regulate gene

expression relevant to cognitive performance via epigenetic mechanisms, including DNA methylation, histone acetylation, and miRNAs (e.g., miR-132, which modulates neurotrophic signaling pathways involved in synaptic plasticity).[120] More investigation into exercise's influence on epigenetics and vice versa is needed to better understand its potential generational cognitive benefits.[4,62,120-122]

(4) **Gut-Brain Axis:** Current clinical evidence indicates that aerobic exercise and resistance training exert distinct effects on gut microbiota composition and neurocognitive outcomes in humans. Aerobic exercise, particularly at moderate intensity and sustained duration (e.g., 150-270 minutes per week for ≥8 weeks), consistently increases gut microbial diversity, augments the abundance of beneficial taxa such as Firmicutes and Akkermansia, and promotes short-chain fatty acid (SCFA) production, which is linked to improved metabolic and cognitive health.[123-126] Aerobic modalities (walking, running, swimming) are associated with enhancements in executive function, memory, and fronto-hippocampal neuroplasticity, with more pronounced cognitive benefits observed in older adults and those with lower baseline fitness.[111,127,128]

Resistance training, while less studied, induces modest changes in gut microbiota composition, notably increasing SCFA-producing genera such as Blautia, without significantly altering overall microbial diversity in short-term interventions.[129] However, resistance training reliably improves executive function, global cognition, and neuroplasticity, potentially via upregulation of neurotrophic factors (e.g., IGF-1), increased gray matter thickness, and reduced hippocampal atrophy.[10,130,131] The cognitive benefits of resistance training are evident across age groups, including older adults and those with cognitive impairment.

Regarding exercise intensity, moderate-intensity aerobic exercise is optimal for gut and brain health, whereas high-intensity interval training may transiently increase intestinal permeability and systemic inflammation, potentially impairing cognitive outcomes.[132-134] Both aerobic and resistance modalities are beneficial, but their effects on the gut-brain axis are mediated by distinct microbial and neurobiological mechanisms. Combining both types may offer additive benefits for cognitive and metabolic health.[10,130]

Current gaps in the literature regarding the beneficial effects of exercise on the gut-brain axis include limited mechanistic understanding, insufficient human interventional data, and a lack of standardized exercise protocols. Most evidence is derived from preclinical or observational studies, with relatively few well-powered randomized controlled trials in humans that directly link exercise-induced changes in gut microbiota to neurocognitive or psychiatric outcomes.[133,135-137] The heterogeneity of study designs, including variations in exercise modality, intensity, duration, and participant characteristics, complicates the interpretation and generalizability of findings.[135,138,139]

Additionally, the precise dose–response relationship between exercise and gut-brain axis modulation remains unclear, and the long-term sustainability of microbiota changes after cessation of exercise is not well established.[133,135,139] There is also a paucity of data on older adults, individuals with comorbidities, and those at risk for neurodegenerative or psychiatric disorders, limiting clinical translation.[136,139] Mediation analyses to confirm causality between microbiota shifts and brain outcomes are rarely performed, and confounding factors such as diet, medication, and baseline fitness are often insufficiently controlled.[136,137] Finally, functional 'omics approaches (e.g., metatranscriptomics, metabolomics) are underutilized, restricting insight into the molecular mechanisms underlying exercise-gut-brain interactions.[133]

(5) **Neuroinflammation and Neurogenesis:** More investigation is needed into how different exercise durations impact neurogenesis in the hippocampus and neuroinflammation.[62]

(6) **Comparative & Long-term Studies:** More studies are needed comparing aerobic and anaerobic exercise, and combinations of the two, in order to determine the most effective exercise strategies for cognitive enhancement. New studies can improve understanding of the dose–response relationship of each form of exercise and specific cognitive enhancements.[4,122]

Potential for Personalized Exercise Interventions

Personalized exercise prescriptions for optimal cognitive benefit can become a reality with more research in the following areas:

(1) **Individualized Exercise Programs**: New studies should aim to determine specific factors that cause specific exercise programs to work for some individuals and not for others. These factors may include genetics, epigenetics, and physiological factors that impact how certain individuals respond to specific exercise programs.

Müllers et al express the need for personalized exercise programs to maximize neuroplastic and preventive effects.[140]

(2) **Combined Aerobic and Anaerobic Exercise**: Future research should focus on how aerobic and anaerobic exercise can optimally be performed together for different individuals. Voss et al notes the importance of both exercise types for preserving brain health in older adults.[122]

(3) **Long-term Effects and Dosage**: More longitudinal studies are needed to better understand the dose–response relationship between different forms of exercise and specific cognitive benefits among different age groups of both men and women.[4]

(4) **Molecular Mechanisms**: More in-depth investigation is needed into the mechanisms through which neurotrophic factors, neurogenesis, and synaptic plasticity lead to cognitive benefits. Nicolini et al express the need for more research in this area to develop effective personalized exercise prescriptions.[141]

(5) **Neuroimaging and Biomarkers**: Identifying new biomarkers and using different neuroimaging techniques can allow researchers to track specific structural and functional brain changes in response to exercise.

(6) **Under-represented Populations**: It's imperative that future research include diverse populations so that findings are generalizable. Researchers such as Boa Sorte Silva et al stress the importance of new research being inclusive of under-represented groups to address cognitive health outcome disparities.[3]

Conclusion

Long-term regular exercise reduces the likelihood of developing cognitive impairment and dementia. Multiple prospective studies show that seniors who perform regular aerobic exercise significantly reduce their risk of dementia and also increase hippocampal size and achieve higher cognitive performance scores.[109] Researchers believe these benefits are due to improved cerebrovascular function, neuroplasticity, and blood flow.[112]

Similarly, regular anaerobic exercise, while supported by less research, promotes neuroplasticity in brain areas susceptible to age-related shrinkage, and has shown to improve memory and executive function.[18] While both improve brain health, exercise routines combining both anaerobic and aerobic elements lead to the most significant cognitive improvements in memory and executive function.[19]

While more research is needed to uncover the molecular mechanisms behind these cognitive benefits, it's evident that exercise increases brain levels of neurotrophic factors, neurogenesis, and the size of brain areas important to memory, such as the hippocampus.[142] These changes are all protective against neurodegenerative disease, and have shown to enhance cognitive functions, such as attention.[143]

Despite exercise's proven ability to promote cognitive resilience and protect against neurodegeneration, more research is still needed to create individualized exercise prescriptions for cognitive benefit. To do so, research is needed to identify individual factors that influence response to exercise, how aerobic and anaerobic exercise can be integrated for optimal results, and the mechanisms behind subsequent brain changes.[4,144-153]

ORCID iD

Cyrus Safaeipour https://orcid.org/0009-0007-5060-854X

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. AJLM

References

1. Kolappa K, Seeher K, Dua T. Brain health as a global priority. *J Neurol Sci*. 2022;439:120326. doi:10.1016/j.jns.2022.120326

2. Navakkode S, Kennedy BK. Neural ageing and synaptic plasticity: prioritizing brain health in healthy longevity. *Front Aging Neurosci*. 2024;16:1428244. doi:10.3389/fnagi.2024.1428244

3. Boa Sorte Silva NC, Barha CK, Erickson KI, Kramer AF, Liu-Ambrose T. Physical exercise, cognition, and brain health in aging. *Trends Neurosci*. 2024;47(6):402-417. doi:10.1016/j.tins.2024.04.004

4. Cabral DF, Rice J, Morris TP, Rundek T, Pascual-Leone A, Gomes-Osman J. Exercise for brain health: an investigation into the underlying mechanisms guided by dose. *Neurotherapeutics*. 2019;16(3):580-599. doi:10.1007/s13311-019-00749-w

5. Lazar RM, Howard VJ, Kernan WN, et al. A primary care agenda for brain health: a scientific statement from the American heart association. *Stroke*. 2021;52(6):e295-e308. doi:10.1161/STR.0000000000000367

6. Powell KE, King AC, Buchner DM, et al. The scientific foundation for the Physical Activity Guidelines for Americans, 2nd edition. *J Phys Act Health*. 2018;17:1-11. doi:10.1123/jpah.2018-0618

7. Augusto-Oliveira M, Arrifano GP, Leal-Nazaré CG, et al. Exercise reshapes the brain: molecular, cellular, and structural changes associated with cognitive improvements. *Mol Neurobiol*. 2023;60(12):6950-6974. doi:10.1007/s12035-023-03492-8

8. Chen C, Nakagawa S. Physical activity for cognitive health promotion: an overview of the underlying

neurobiological mechanisms. *Ageing Res Rev*. 2023;86:101868. doi:10.1016/j.arr.2023.101868

9. Zwilling CE, Talukdar T, Zamroziewicz MK, Barbey AK. Nutrient biomarker patterns, cognitive function, and fMRI measures of network efficiency in the aging brain. *Neuroimage*. 2019;188:239-251. doi:10.1016/j.neuroimage.2018.12.007
10. Chow ZS, Moreland AT, Macpherson H, Teo WP. The central mechanisms of resistance training and its effects on cognitive function. *Sports Med*. 2021;51(12):2483-2506. doi:10.1007/s40279-021-01535-5
11. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci*. 2003;14(2):125-130. doi:10.1111/1467-9280.t01-1-01430
12. Cantelon JA, Giles GE. A review of cognitive changes during acute aerobic exercise. *Front Psychol*. 2021;12:653158. doi:10.3389/fpsyg.2021.653158
13. Carro E, Nuñez A, Busiguina S, Torres-Aleman I. Circulating insulin-like growth factor I mediates effects of exercise on the brain. *J Neurosci*. 2000;20(8):2926-2933. doi:10.1523/JNEUROSCI.20-08-02926.2000
14. Carroll TJ, Barry B, Riek S, Carson RG. Resistance training enhances the stability of sensorimotor coordination. *Proc Biol Sci*. 2001;268(1464):221-227. doi:10.1098/rspb.2000.1356
15. Cefis M, Chaney R, Wirtz J, et al. Molecular mechanisms underlying physical exercise-induced brain BDNF overproduction. *Front Mol Neurosci*. 2023;16:1275924. doi:10.3389/fnmol.2023.1275924
16. Cespón J, Miniussi C, Pellicciari MC. Interventional programmes to improve cognition during healthy and pathological ageing: cortical modulations and evidence for brain plasticity. *Ageing Res Rev*. 2018;43:81-98. doi:10.1016/j.arr.2018.03.001
17. Chen AG, Zhu LN, Yan J, Yin HC. Neural basis of working memory enhancement after acute aerobic exercise: fMRI study of preadolescent children. *Front Psychol*. 2016;7:1804. doi:10.3389/fpsyg.2016.01804
18. Karamacoska D, Butt A, Leung IHK, et al. Brain function effects of exercise interventions for cognitive decline: a systematic review and meta-analysis. *Front Neurosci*. 2023;17:1127065. doi:10.3389/fnins.2023.1127065
19. Jonasson LS, Nyberg L, Kramer AF, Lundquist A, Riklund K, Boraxbekk CJ. Aerobic exercise intervention, cognitive performance, and brain structure: results from the Physical Influences on Brain in Aging (PHIBRA) Study. *Front Aging Neurosci*. 2017;8:336. doi:10.3389/fnagi.2016.00336
20. Yogev-Seligmann G, Eisenstein T, Ash E, et al. Neurocognitive plasticity is associated with cardiorespiratory fitness following physical exercise in older adults with amnestic mild cognitive impairment. *J Alzheimers Dis*. 2021;81(1):91-112. doi:10.3233/JAD-201429
21. Jia Y, Yao Y, Zhuo L, et al. Aerobic physical exercise as a non-medical intervention for brain dysfunction: state of the art and beyond. *Front Neurol*. 2022;13:862078. doi:10.3389/fneur.2022.862078
22. Kandola A, Hendrikse J, Lucassen PJ, Yücel M. Aerobic exercise as a tool to improve hippocampal plasticity and function in humans: practical implications for mental health treatment. *Front Hum Neurosci*. 2016;10:373. doi:10.3389/fnhum.2016.00373
23. Erwin H, Schreiber S. Aerobic and anaerobic exercise's impact on cognitive functions in eighth grade students. *Int J Environ Res Public Health*. 2024;21(7):833. doi:10.3390/ijerph21070833
24. Zhang K, Jan YK, Liu Y, et al. Exercise intensity and brain plasticity: what's the difference of brain structural and functional plasticity characteristics between elite aerobic and anaerobic athletes? *Front Hum Neurosci*. 2022;16:757522. doi:10.3389/fnhum.2022.757522
25. Hamilton GF, Rhodes JS. Exercise regulation of cognitive function and neuroplasticity in the healthy and diseased brain. *Prog Mol Biol Transl Sci*. 2015;135:381-406.
26. Mahalakshmi B, Maurya N, Lee SD, Bharath Kumar V. Possible neuroprotective mechanisms of physical exercise in neurodegeneration. *Int J Mol Sci*. 2020;21(16):5895. doi:10.3390/ijms21165895
27. Sanaeifar F, Pourranjbar S, Pourranjbar M, et al. Beneficial effects of physical exercise on cognitive-behavioral impairments and brain-derived neurotrophic factor alteration in the limbic system induced by neurodegeneration. *Exp Gerontol*. 2024;195:112539. doi:10.1016/j.exger.2024.112539
28. Arida RM, Teixeira-Machado L. The contribution of physical exercise to brain resilience. *Front Behav Neurosci*. 2021;14:626769. doi:10.3389/fnbeh.2020.626769
29. Hötting K, Röder B. Beneficial effects of physical exercise on neuroplasticity and cognition. *Neurosci Biobehav Rev*. 2013;37(9 Pt B):2243-2257. doi:10.1016/j.neubiorev.2013.04.005
30. Liang J, Wang H, Zeng Y, et al. Physical exercise promotes brain remodeling by regulating epigenetics, neuroplasticity and neurotrophins. *Rev Neurosci*. 2021;32(6):615-629. doi:10.1515/revneuro-2020-0099
31. Liu Y, Yan T, Chu JM, et al. The beneficial effects of physical exercise in the brain and related pathophysiological mechanisms in neurodegenerative diseases. *Lab Invest*. 2019;99(7):943-957. doi:10.1038/s41374-019-0232-y
32. Sujkowski A, Hong L, Wessells RJ, Todi SV. The protective role of exercise against age-related neurodegeneration. *Ageing Res Rev*. 2022;74:101543. doi:10.1016/j.arr.2021.101543
33. Chen Y, Demnitz N, Yamamoto S, Yaffe K, Lawlor B, Leroi I. Defining brain health: a concept analysis. *Int J Geriatr Psychiatry*. 2022;37:1-13. doi:10.1002/gps.5564. Published online April 30.
34. Harerimana B, Forchuk C, Walsh J, Fogarty J, Borrie M. Brain health: a concept analysis. *Issues Ment Health Nurs*. 2021;42(2):145-152. doi:10.1080/01612840.2020.1789781
35. Gorelick PB, Furie KL, Iadecola C, et al. Defining optimal brain health in adults: a presidential advisory from the American heart Association/American Stroke Association. *Stroke*. 2017;48(10):e284-e303. doi:10.1161/STR.0000000000000148
36. Stern Y. How can cognitive reserve promote cognitive and neurobehavioral health? *Arch Clin Neuropsychol*. 2021;36(7):1291-1295. doi:10.1093/arclin/acab049
37. Jackson PA, Pialoux V, Corbett D, et al. Promoting brain health through exercise and diet in older adults:

a physiological perspective. *J Physiol*. 2016;594(16):4485-4498. doi:10.1113/JP271270

38. Colucci-D'Amato L, Speranza L, Volpicelli F. Neurotrophic factor BDNF, physiological functions and therapeutic potential in depression, neurodegeneration and brain cancer. *Int J Mol Sci*. 2020;21(20):7777. doi:10.3390/ijms21207777
39. Rothman SM, Mattson MP. Activity-dependent, stress-responsive BDNF signaling and the quest for optimal brain health and resilience throughout the lifespan. *Neuroscience*. 2013;239:228-240. doi:10.1016/j.neuroscience.2012.10.014
40. Begni V, Riva MA, Cattaneo A. Cellular and molecular mechanisms of the brain-derived neurotrophic factor in physiological and pathological conditions. *Clin Sci*. 2017;131(2):123-138. doi:10.1042/CS20160009
41. Gray JD, Milner TA, McEwen BS. Dynamic plasticity: the role of glucocorticoids, brain-derived neurotrophic factor and other trophic factors. *Neuroscience*. 2013;239:214-227. doi:10.1016/j.neuroscience.2012.08.034
42. von Bohlen Und Halbach O, von Bohlen Und Halbach V. BDNF effects on dendritic spine morphology and hippocampal function. *Cell Tissue Res*. 2018;373(3):729-741. doi:10.1007/s00441-017-2782-x
43. Feter N, Ligeza TS, Bashir N, et al. Effects of reducing sedentary behaviour by increasing physical activity, on cognitive function, brain function and structure across the lifespan: a systematic review and meta-analysis. *Br J Sports Med*. 2024;58(21):1295-1306. doi:10.1136/bjsports-2024-108444
44. Han X, Song L, Li Y, et al. Accelerometer-measured sedentary behavior patterns, brain structure, and cognitive function in dementia-free older adults: a population-based study. *J Alzheimers Dis*. 2023;96(2):657-668. doi:10.3233/JAD-230575
45. Siddarth P, Burggren AC, Eyre HA, Small GW, Merrill DA. Sedentary behavior associated with reduced medial temporal lobe thickness in middle-aged and older adults. *PLoS One*. 2018;13(4):e0195549. doi:10.1371/journal.pone.0195549
46. Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A*. 2011;108(7):3017-3022. doi:10.1073/pnas.1015950108
47. Steventon JJ, Foster C, Furby H, Helme D, Wise RG, Murphy K. Hippocampal blood flow is increased after 20 min of moderate-intensity exercise. *Cereb Cortex*. 2020;30(2):525-533. doi:10.1093/cercor/bhz104
48. Maass A, Düzel S, Goerke M, et al. Vascular hippocampal plasticity after aerobic exercise in older adults. *Mol Psychiatry*. 2015;20(5):585-593. doi:10.1038/mp.2014.114
49. Stimpson NJ, Davison G, Javadi AH. Joggin' the noggin: towards a physiological understanding of exercise-induced cognitive benefits. *Neurosci Biobehav Rev*. 2018;88:177-186. doi:10.1016/j.neubiorev.2018.03.018
50. El Hayek L, Khalifeh M, Zibara V, 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(13):2369-2382. doi:10.1523/JNEUROSCI.1661-18.2019
51. Maejima H, Kanemura N, Kokubun T, Murata K, Takayanagi K. Exercise enhances cognitive function and neurotrophin expression in the hippocampus accompanied by changes in epigenetic programming in senescence-accelerated mice. *Neurosci Lett*. 2018;665:67-73. doi:10.1016/j.neulet.2017.11.023
52. Pietrelli A, Matković L, Vacotto M, Lopez-Costa JJ, Basso N, Brusco A. Aerobic exercise upregulates the BDNF-serotonin systems and improves the cognitive function in rats. *Neurobiol Learn Mem*. 2018;155:528-542. doi:10.1016/j.nlm.2018.05.007
53. Wang R, Holsinger RMD. Exercise-induced brain-derived neurotrophic factor expression: therapeutic implications for Alzheimer's dementia. *Ageing Res Rev*. 2018;48:109-121. doi:10.1016/j.arr.2018.10.002
54. Choi JW, Jo SW, Kim DE, Paik IY, Balakrishnan R. Aerobic exercise attenuates LPS-induced cognitive dysfunction by reducing oxidative stress, glial activation, and neuroinflammation. *Redox Biol*. 2024;71:103101. doi:10.1016/j.redox.2024.103101
55. Marosi K, Bori Z, Hart N, et al. Long-term exercise treatment reduces oxidative stress in the hippocampus of aging rats. *Neuroscience*. 2012;226:21-28. doi:10.1016/j.neuroscience.2012.09.001
56. Xie G, Xu Z, Li F, Kong M, Wang P, Shao Y. Aerobic exercise ameliorates cognitive disorder and declined oxidative stress via modulating the Nrf2 signaling pathway in D-galactose induced aging mouse model. *Neurochem Res*. 2024;49(9):2408-2422. doi:10.1007/s11064-024-04164-2
57. Liu Y, Meng X, Tang C, Zheng L, Tao K, Guo W. Aerobic exercise modulates RIPK1-mediated MAP3K5/JNK and NF-κB pathways to suppress microglia activation and neuroinflammation in the hippocampus of D-gal-induced accelerated aging mice. *Physiol Behav*. 2024;286:114676. doi:10.1016/j.physbeh.2024.114676
58. Mu L, Xia D, Cai J, et al. Treadmill exercise reduces neuroinflammation, glial cell activation and improves synaptic transmission in the prefrontal cortex in 3 × Tg-AD mice. *Int J Mol Sci*. 2022;23(20):12655. doi:10.3390/ijms232012655
59. Pahlavani HA. Exercise therapy to prevent and treat Alzheimer's disease. *Front Aging Neurosci*. 2023;15:1243869. doi:10.3389/fnagi.2023.1243869
60. Cutuli D, Decandia D, Giacovazzo G, Coccurello R. Physical exercise as disease-modifying alternative against Alzheimer's Disease: a gut-muscle-brain partnership. *Int J Mol Sci*. 2023;24(19):14686. doi:10.3390/ijms241914686
61. Pedersen BK. Physical activity and muscle-brain crosstalk. *Nat Rev Endocrinol*. 2019;15(7):383-392. doi:10.1038/s41574-019-0174-x
62. Connolly MG, Bruce SR, Kohman RA. Exercise duration differentially effects age-related neuroinflammation and hippocampal neurogenesis. *Neuroscience*. 2022;490:275-286. doi:10.1016/j.neuroscience.2022.03.022
63. Tallent J, Woodhead A, Frazer AK, Hill J, Kidgell DJ, Howatson G. Corticospinal and spinal adaptations to motor skill and resistance training: potential mechanisms and implications for motor rehabilitation and athletic development. *Eur J Appl Physiol*. 2021;121(3):707-719. doi:10.1007/s00421-020-04584-2

64. Niu X, Zhao Y, Yang N, et al. Proteasome activation by insulin-like growth factor-1/nuclear factor erythroid 2-related factor 2 signaling promotes exercise-induced neurogenesis. *Stem Cells*. 2020;38(2): 246-260. doi:10.1002/stem.3102

65. Kraemer RR, Kraemer BR. The effects of peripheral hormone responses to exercise on adult hippocampal neurogenesis. *Front Endocrinol (Lausanne)*. 2023;14:1202349. doi:10.3389/fendo.2023.1202349

66. Alizadeh PH. Possible role of exercise therapy on depression: effector neurotransmitters as key players. *Behav Brain Res*. 2024;459:114791. doi:10.1016/j.bbr.2023.114791

67. Barahona-Fuentes G, Huerta Ojeda Á, Chirosa-Ríos L. Effects of training with different modes of strength intervention on psychosocial disorders in adolescents: a systematic review and meta-analysis. *Int J Environ Res Public Health*. 2021; 18(18):9477. doi:10.3390/ijerph18189477

68. Gordon BR, McDowell CP, Lyons M, Herring MP. The effects of resistance exercise training on anxiety: a meta-analysis and meta-regression analysis of randomized controlled trials. *Sports Med*. 2017;47(12):2521-2532. doi:10.1007/s40279-017-0769-0

69. Strickland JC, Smith MA. The anxiolytic effects of resistance exercise. *Front Psychol*. 2014;5:753. doi:10.3389/fpsyg.2014.00753

70. Nauer RK, Dunne MF, Stern CE, Storer TW, Schon K. Improving fitness increases dentate gyrus/CA3 volume in the hippocampal head and enhances memory in young adults. *Hippocampus*. 2020;30(5):488-504. doi:10.1002/hipo.23166

71. Prathap S, Nagel BJ, Herting MM. Understanding the role of aerobic fitness, spatial learning, and hippocampal subfields in adolescent males. *Sci Rep*. 2021;11(1):9311. doi: 10.1038/s41598-021-88452-9

72. Griffin ÉW, Mullally S, Foley C, Warmington SA, O'Mara SM, Kelly AM. Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiol Behav*. 2011;104(5): 934-941. doi:10.1016/j.physbeh.2011.06.005

73. Hwang J, Brothers RM, Castelli DM, et al. Acute high-intensity exercise-induced cognitive enhancement and brain-derived neurotrophic factor in young, healthy adults. *Neurosci Lett*. 2016;630:247-253. doi:10.1016/j.neulet.2016.07.033

74. Bae S, Masaki H. Effects of acute aerobic exercise on cognitive flexibility required during task-switching paradigm. *Front Hum Neurosci*. 2019;13:260. doi:10.3389/fnhum.2019.00260

75. Heath M, Shukla D. A single bout of aerobic exercise provides an immediate "Boost" to cognitive flexibility. *Front Psychol*. 2020;11: 1106. doi:10.3389/fpsyg.2020.01106

76. Shukla D, Al-Shamil Z, Belfry G, Heath M. A single bout of moderate intensity exercise improves cognitive flexibility: evidence from task-switching. *Exp Brain Res*. 2020; 238(10):2333-2346. doi:10.1007/s00221-020-05885-w

77. Li L, Men WW, Chang YK, Fan MX, Ji L, Wei GX. Acute aerobic exercise increases cortical activity during working memory: a functional MRI study in female college students. *PLoS One*. 2014;9(6):e99222. doi:10.1371/journal.pone.0099222

78. Morris TP, Fried PJ, Macone J, et al. Light aerobic exercise modulates executive function and cortical excitability. *Eur J Neurosci*. 2020; 51(7):1723-1734. doi:10.1111/ejn.14593

79. Tari B, Vanhie JJ, Belfry GR, Shoemaker JK, Heath M. Increased cerebral blood flow supports a single-bout postexercise benefit to executive function: evidence from hypercapnia. *J Neurophysiol*. 2020;124(3):930-940. doi:10.1152/jn.00240.2020

80. Ye M, Song T, Xia H, Hou Y, Chen A. Effects of aerobic exercise on executive function of healthy middle-aged and older adults: a systematic review and meta-analysis. *Int J Nurs Stud*. 2024;160:104912. doi:10.1016/j.ijnurstu.2024.104912

81. Morris JK, Vidoni ED, Johnson DK, et al. Aerobic exercise for Alzheimer's disease: a randomized controlled pilot trial. *PLoS One*. 2017;12(2): e0170547. doi:10.1371/journal.pone.0170547

82. Martini M, Enoch J, Kramer AF. The effects of a short exercise bout on executive functions in healthy older adults. *Sci Rep*. 2024;14(1):28827. doi: 10.1038/s41598-024-79685-5

83. Zhou YS, Meng FC, Cui Y, et al. Regular aerobic exercise attenuates pain and anxiety in mice by restoring serotonin-modulated synaptic plasticity in the anterior Cingulate cortex. *Med Sci Sports Exerc*. 2022; 54(4):566-581. doi:10.1249/MSS.0000000000002841

84. Zschucke E, Renneberg B, Dimeo F, Wüstenberg T, Ströhle A. The stress-buffering effect of acute exercise: evidence for HPA axis negative feedback. *Psychoneuroendocrinology*. 2015;51: 414-425. doi:10.1016/j.psyneuen.2014.10.019

85. Hare BD, Beierle JA, Toufexis DJ, Hammack SE, Falls WA. Exercise-associated changes in the corticosterone response to acute restraint stress: evidence for increased adrenal sensitivity and reduced corticosterone response duration. *Neuropsychopharmacology*. 2014; 39(5):1262-1269. doi:10.1038/npp.2013.329

86. LeBouthillier DM, Asmundson GJG. The efficacy of aerobic exercise and resistance training as transdiagnostic interventions for anxiety-related disorders and constructs: a randomized controlled trial. *J Anxiety Disord*. 2017;52:43-52. doi: 10.1016/j.janxdis.2017.09.005

87. Herring MP, Meyer JD. Resistance exercise for anxiety and depression: efficacy and plausible mechanisms. *Trends Mol Med*. 2024;30(3):204-206. doi:10.1016/j.molmed.2023.11.016

88. Kanaley JA, Colberg SR, Corcoran MH, et al. Exercise/Physical activity in individuals with type 2 diabetes: a consensus statement from the American college of sports medicine. *Med Sci Sports Exerc*. 2022;54(2): 353-368. doi:10.1249/MSS.0000000000002800

89. da Costa TS, Seffrin A, de Castro Filho J, et al. Effects of aerobic and strength training on depression, anxiety, and health self-perception levels during the COVID-19 pandemic. *Eur Rev Med Pharmacol Sci*. 2022;26(15): 5601-5610. doi:10.26355/eurrev_202208_29433

90. Kaufman CS, Honea RA, Pleen J, et al. Aerobic exercise improves hippocampal blood flow for hypertensive Apolipoprotein E4 carriers. *J Cereb Blood Flow Metab*. 2021;41(8):2026-2037. doi:10.1177/0271678X21990342

91. Thomas BP, Tarumi T, Sheng M, et al. Brain perfusion change in patients with mild cognitive impairment after

12 months of aerobic exercise training. *J Alzheimers Dis*. 2020;75(2):617-631. doi:10.3233/JAD-190977

92. Broadhouse KM, Singh MF, Suo C, et al. Hippocampal plasticity underpins long-term cognitive gains from resistance exercise in MCI. *Neuroimage Clin*. 2020;25:102182. doi:10.1016/j.nicl.2020.102182
93. Nicola L, Loo SJQ, Lyon G, Turknett J, Wood TR. Does resistance training in older adults lead to structural brain changes associated with a lower risk of Alzheimer's dementia? A narrative review. *Ageing Res Rev*. 2024;98:102356. doi:10.1016/j.arr.2024.102356
94. Suo C, Singh MF, Gates N, et al. Therapeutically relevant structural and functional mechanisms triggered by physical and cognitive exercise. *Mol Psychiatry*. 2016;21(11):1633-1642. doi:10.1038/mp.2016.19
95. Best JR, Chiu BK, Liang Hsu C, Nagamatsu LS, Liu-Ambrose T. Long-Term effects of resistance exercise training on cognition and brain volume in older women: results from a randomized controlled trial. *J Int Neuropsychol Soc*. 2015;21(10):745-756. doi:10.1017/S1355617715000673
96. Chen YH, Kuo TT, Kao JH, et al. Exercise ameliorates motor deficits and improves dopaminergic functions in the rat hemi-parkinson's model. *Sci Rep*. 2018;8(1):3973. doi:10.1038/s41598-018-22462-y
97. Sacheli MA, Neva JL, Lakhani B, et al. Exercise increases caudate dopamine release and ventral striatal activation in Parkinson's disease. *Mov Disord*. 2019;34(12):1891-1900. doi:10.1002/mds.27865
98. Wang X, Wang Y, Chen J, Li J, Liu Y, Chen W. Aerobic exercise improves motor function and striatal MSNs-Erk/MAPK signaling in mice with 6-OHDA-induced Parkinson's disease. *Exp Brain Res*. 2022;240(6):1713-1725. doi:10.1007/s00221-022-06360-4
99. Johansson ME, Cameron IGM, Van der Kolk NM, et al. Aerobic exercise alters brain function and structure in Parkinson's disease: a randomized controlled trial. *Ann Neurol*. 2022;91(2):203-216. doi:10.1002/ana.26291
100. Petzinger GM, Fisher BE, McEwen S, Beeler JA, Walsh JP, Jakowec MW. Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in parkinson's disease. *Lancet Neurol*. 2013;12(7):716-726. doi:10.1016/S1474-4422(13)70123-6
101. Helgerud J, Thomsen SN, Hoff J, et al. Maximal strength training in patients with Parkinson's disease: impact on efferent neural drive, force-generating capacity, and functional performance. *J Appl Physiol*. 2020;129(4):683-690. doi:10.1152/japplphysiol.00208.2020
102. Silva-Batista C, Corcos DM, Kanegusuku H, et al. Balance and fear of falling in subjects with Parkinson's disease is improved after exercises with motor complexity. *Gait Posture*. 2018;61:90-97. doi:10.1016/j.gaitpost.2017.12.027
103. Strand KL, Cherup NP, Totillo MC, Castillo DC, Gabor NJ, Signorile JF. Periodized resistance training with and without functional training improves functional capacity, balance, and strength in Parkinson's disease. *J Strength Cond Res*. 2021;35(6):1611-1619. doi:10.1519/JSC.0000000000004025
104. Morris ME, Menz HB, McGinley JL, et al. A randomized controlled trial to reduce falls in people with Parkinson's disease. *Neurorehabil Neural Repair*. 2015;29(8):777-785. doi:10.1177/1545968314565511
105. Liu S, Yu Q, Li Z, et al. Effects of acute and chronic exercises on executive function in children and adolescents: a systemic review and meta-analysis. *Front Psychol*. 2020;11:554915. doi:10.3389/fpsyg.2020.554915
106. Li JW, O'Connor H, O'Dwyer N, Orr R. The effect of acute and chronic exercise on cognitive function and academic performance in adolescents: a systematic review. *J Sci Med Sport*. 2017;20(9):841-848. doi:10.1016/j.jsams.2016.11.025
107. Ferreira Vorkapic C, Alves H, Araujo L, et al. Does physical activity improve cognition and academic performance in children? A systematic review of randomized controlled trials. *Neuropsychobiology*. 2021;80(6):454-482. doi:10.1159/000514682
108. Davis CL, Tomporowski PD, McDowell JE, et al. Exercise improves executive function and achievement and alters brain activation in overweight children: a randomized, controlled trial. *Health Psychol*. 2011;30(1):91-98. doi:10.1037/a0021766
109. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. *Mayo Clin Proc*. 2011;86(9):876-884. doi:10.4065/mcp.2011.0252
110. American College of Sports Medicine. Chodzko-Zajko WJ, Proctor DN, et al. American College of Sports Medicine position stand. Exercise and physical activity for older adults. *Med Sci Sports Exerc*. 2009;41(7):1510-1530. doi:10.1249/MSS.0b013e3181a0c95c
111. Guadagni V, Drogos LL, Tyndall AV, et al. Aerobic exercise improves cognition and cerebrovascular regulation in older adults. *Neurology*. 2020;94(21):e2245-e2257. doi:10.1212/WNL.0000000000009478
112. Bliss ES, Wong RH, Howe PR, Mills DE. Benefits of exercise training on cerebrovascular and cognitive function in ageing. *J Cereb Blood Flow Metab*. 2021;41(3):447-470. doi:10.1177/0271678X20957807
113. Xu L, Gu H, Cai X, et al. The effects of exercise for cognitive function in older adults: a systematic review and meta-analysis of randomized controlled trials. *Int J Environ Res Public Health*. 2023;20(2):1088. doi:10.3390/ijerph20021088
114. Steves CJ, Mehta MM, Jackson SH, Spector TD. Kicking back cognitive ageing: leg power predicts cognitive ageing after ten years in older female twins. *Gerontology*. 2016;62(2):138-149. doi:10.1159/000441029
115. Panza GA, Taylor BA, MacDonald HV, et al. Can exercise improve cognitive symptoms of Alzheimer's disease? *J Am Geriatr Soc*. 2018;66(3):487-495. doi:10.1111/jgs.15241
116. Li Z, Guo H, Liu X. What exercise strategies are best for people with cognitive impairment and dementia? A systematic review and meta-analysis. *Arch Gerontol Geriatr*. 2024;124:105450. doi:10.1016/j.archger.2024.105450
117. Stillman CM, Esteban-Cornejo I, Brown B, Bender CM, Erickson KI. Effects of exercise on brain and cognition across age groups and health states. *Trends Neurosci*. 2020;43(7):533-543. doi:10.1016/j.tins.2020.04.010
118. Burtscher J, Millet GP, Place N, Kayser B, Zanou N. The muscle-brain axis and neurodegenerative diseases: the key role of Mitochondria in exercise-induced neuroprotection. *Int J Mol Sci*. 2021;22(12):6479. doi:10.3390/ijms22126479

119. De la Rosa A, Solana E, Corpas R, et al. Long-term exercise training improves memory in middle-aged men and modulates peripheral levels of BDNF and Cathepsin B. *Sci Rep*. 2019;9(1):3337. doi:10.1038/s41598-019-40040-8

120. Zhang R, Liu S, Mousavi SM. Cognitive dysfunction and exercise: from epigenetic to genetic molecular mechanisms. *Mol Neurobiol*. 2024;61(9):6279-6299. doi:10.1007/s12035-024-03970-7

121. Kukla-Bartoszek M, Głombik K. Train and reprogram your brain: effects of physical exercise at different stages of life on brain functions saved in epigenetic modifications. *Int J Mol Sci*. 2024;25(22):12043. doi:10.3390/ijms252212043

122. Voss MW, Nagamatsu LS, Liu-Ambrose T, Kramer AF. Exercise, brain, and cognition across the life span. *J Appl Physiol (1985)*. 2011;111(5):1505-1513. doi:10.1152/japplphysiol.00210.2011

123. Boytar AN, Skinner TL, Wallen RE, Jenkins DG, Nitert MD. The effect of exercise prescription on the human gut microbiota and comparison between clinical and apparently healthy populations: a systematic review. *Nutrients*. 2023;15(6):1534. doi:10.3390/nu15061534

124. Hintikka JE, Ahtiainen JP, Permi P, Jalkanen S, Lehtonen M, Pekkala S. Aerobic exercise training and gut microbiome-associated metabolic shifts in women with overweight: a multi-omic study. *Sci Rep*. 2023;13(1):11228. doi:10.1038/s41598-023-38357-6

125. Min L, Ablitip A, Wang R, Luciana T, Wei M, Ma X. Effects of exercise on gut microbiota of adults: a systematic review and meta-analysis. *Nutrients*. 2024;16(7):1070. doi:10.3390/nu16071070

126. Wei C, Wu X, Li C, Zhang Y, Yuan Q, Huang R. Aerobic exercise regulates gut microbiota profiles and metabolite in the early stage of Alzheimer's disease. *FASEB J*. 2025;39(2):e70327. doi:10.1096/fj.202402572R

127. Serra L, Petrosini L, Mandolesi L, et al. Walking, running, swimming: an analysis of the effects of land and water aerobic exercises on cognitive functions and neural substrates. *Int J Environ Res Public Health*. 2022;19(23):16310. doi:10.3390/ijerph192316310

128. Stern Y, MacKay-Brandt A, Lee S, et al. Effect of aerobic exercise on cognition in younger adults: a randomized clinical trial. *Neurology*. 2019;92(9):e905-e916. doi:10.1212/WNL.0000000000007003

129. Cullen JMA, Shahzad S, Kanaley JA, Ericsson AC, Dhillon J. The effects of 6 wk of resistance training on the gut microbiome and cardiometabolic health in young adults with overweight and obesity. *J Appl Physiol (1985)*. 2024;136(2):349-361. doi:10.1152/japplphysiol.00350.2023

130. Jiang W, Wang X, Mao L. Effects of resistance exercise on cognitive function, neurotrophic factors, brain structure, and brain function in older adults: a narrative review. *J Alzheimers Dis*. 2025;107(1):15-38. doi:10.1177/13872877251359630

131. Landrigan JF, Bell T, Crowe M, Clay OJ, Mirman D. Lifting cognition: a meta-analysis of effects of resistance exercise on cognition. *Psychol Res*. 2020;84(5):1167-1183. doi:10.1007/s00426-019-01145-x

132. Cintado E, Muela P, Martín-Rodríguez L, et al. Gut microbiota regulates exercise-induced hormetic modulation of cognitive function. *EBioMedicine*. 2025;119:105876. doi:10.1016/j.ebiom.2025.105876

133. Hawley JA, Forster SC, Giles EM. Exercise, the gut microbiome and gastrointestinal diseases: therapeutic impact and molecular mechanisms. *Gastroenterology*. 2025;169(1):48-62. doi:10.1053/j.gastro.2025.01.224

134. Peng M, Zou R, Yao S, et al. High-intensity interval training and medium-intensity continuous training may affect cognitive function through regulation of intestinal microbial composition and its metabolite LPS by the gut-brain axis. *Life Sci*. 2024;352:122871. doi:10.1016/j.lfs.2024.122871

135. Cataldi S, Poli L, Şahin FN, et al. The effects of physical activity on the gut microbiota and the gut-brain axis in preclinical and human models: a narrative review. *Nutrients*. 2022;14(16):3293. doi:10.3390/nu14163293

136. Koblinsky ND, Power KA, Middleton L, Ferland G, Anderson ND. The role of the gut microbiome in diet and exercise effects on cognition: a review of the intervention literature. *J Gerontol A Biol Sci Med Sci*. 2023;78(2):195-205. doi:10.1093/gerona/glac166

137. Zhang L, Liu R, Song Z, Zhang X. Exercise, diet, and brain health: from the perspective of gut microbiota regulation. *Nutrients*. 2025;17(10):1686. doi:10.3390/nu17101686

138. Al-Beltagi M, Saeed NK, Bediwy AS, El-Sawaf Y, Elbatarny A, Elbeltagi R. Exploring the gut-exercise link: a systematic review of gastrointestinal disorders in physical activity. *World J Gastroenterol*. 2025;31(22):106835. doi:10.3748/wjg.v31.i22.106835

139. Tari AR, Walker TL, Huuha AM, Sando SB, Wisloff U. Neuroprotective mechanisms of exercise and the importance of fitness for healthy brain ageing. *Lancet*. 2025;405(10484):1093-1118. doi:10.1016/S0140-6736(25)00184-9

140. Müllers P, Taubert M, Müller NG. Physical exercise as personalized medicine for dementia prevention? *Front Physiol*. 2019;10:672. doi:10.3389/fphys.2019.00672

141. Nicolini C, Fahnestock M, Gibala MJ, Nelson AJ. Understanding the neurophysiological and molecular mechanisms of exercise-induced neuroplasticity in cortical and descending motor pathways: where do we stand? *Neuroscience*. 2021;457:259-282. doi:10.1016/j.neuroscience.2020.12.013

142. Gomez-Pinilla F, Hillman C. The influence of exercise on cognitive abilities. *Compr Physiol*. 2013;3(1):403-428. doi:10.1002/cphy.c110063

143. Dunsky A, Abu-Rukun M, Tsuk S, Dwolatzky T, Carasso R, Netz Y. The effects of a resistance vs. an aerobic single session on attention and executive functioning in adults [published correction appears in PLoS One. 2017 Jun 12;12(6):e0179799. doi: 10.1371/journal.pone.0179799]. *PLoS One*. 2017;12(4):e0176092. doi:10.1371/journal.pone.0176092

144. Abavisani M, Faraji N, Ebadpour N, Kesharwani P, Sahebkar A. Beyond digestion: exploring how the gut microbiota modulates human social behaviors. *Neuroscience*. 2025;565:52-62. doi:10.1016/j.neuroscience.2024.11.068

145. Athanasiou N, Bogdanis GC, Mastorakos G. Endocrine responses of the stress system to different types of exercise. *Rev Endocr Metab Disord*. 2023;24(2):251-266. doi:10.1007/s11154-022-09758-1

146. Dicks LMT. Our mental health is determined by an intrinsic interplay

between the central nervous system, enteric nerves, and Gut Microbiota. *Int J Mol Sci*. 2023;25(1):38. doi:10.3390/ijms25010038

147. Hwang YK, Oh JS. Interaction of the vagus nerve and serotonin in the gut-brain axis. *Int J Mol Sci*. 2025;26(3):1160. doi:10.3390/ijms26031160
148. Kim S, Choi JY, Moon S, Park DH, Kwak HB, Kang JH. Roles of myokines in exercise-induced improvement of neuropsychiatric function. *Pflugers Arch*. 2019;471(3):491-505. doi:10.1007/s00424-019-02253-8
149. Moţăţăianu A, Şerban G, Andone S. The role of short-chain fatty acids in microbiota-gut-brain cross-talk with a focus on amyotrophic lateral sclerosis: a systematic review. *Int J Mol Sci*. 2023;24(20):15094. doi:10.3390/ijms242015094
150. Nowacka-Chmielewska M, Grabowska K, Grabowski M, Meybohm P, Burek M, Małecki A. Running from stress: neurobiological mechanisms of exercise-induced stress resilience. *Int J Mol Sci*. 2022;23(21):13348. doi:10.3390/ijms232113348
151. O'Riordan KJ, Collins MK, Moloney GM, et al. Short chain fatty acids: microbial metabolites for gut-brain axis signalling. *Mol Cell Endocrinol*. 2022;546:111572. doi:10.1016/j.mce.2022.111572
152. Palmer JA, Morris JK, Billinger SA, et al. Hippocampal blood flow rapidly and preferentially increases after a bout of moderate-intensity exercise in older adults with poor cerebrovascular health. *Cereb Cortex*. 2023;33(9):5297-5306. doi:10.1093/cercor/bhac418
153. Umegaki H, Sakurai T, Arai H. Active life for brain health: a narrative review of the mechanism underlying the protective effects of physical activity on the brain. *Front Aging Neurosci*. 2021;13:761674. doi:10.3389/fnagi.2021.761674